CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212937Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	212937		
Applicant Name	FENNEC PHARMACEUTICALS INC		
Drug Product Name	PEDMARK® (sodium thiosulfate injection)		
Dosage Form.	Injection		
Proposed Strength(s)	12.5 grams/100 mL		
Route of Administration	Intravenous		
Maximum Daily Dose	23 g/day		
Rx/OTC Dispensed	Rx		
Proposed Indication	PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin-based chemotherapy in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.		
Drug Product Description	Clear, colorless solution in a single-dose vial		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F). An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Paresma Patel	Paresma Patel
	Drug Product/ Labeling	Tefsit Bekele	Xing Wang

	Manufacturing	Steven Hertz	Yiwei Li
	Biopharmaceutics	N/A	N/A
	Microbiology	Bernard Marasa	Julie Nemecek
	Other (specify):	None	None
	RBPM	Rabiya Haider	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - *APPROVAL*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

NDA 212937 received two Complete Response letters (08/10/2020, 11/26/2021) mainly due to facility inspection and manufacturing processes issues. The applicant withdrew the (b) (4) *and replaced it with Berkshire Sterile Manufacturing (BSM) as the drug product manufacturer in this resubmission (03/23/2022). A PAI was conducted at BSM. OPMA evaluated the inspection outcome and the additional process hold time information and deems the manufacturing process and facilities information as adequate.*

OPQ recommends **APPROVAL** *of NDA 212737. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include 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	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

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

5. Life-Cycle Considerations

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

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

Additional Lifecycle Comments: None

Xing Wang

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	212937
Assessment Cycle Number	#3
Drug Product Name/ Strength	Sodium thiosulfate (b) (4) mg/mL
Route of Administration	Intravenous (b) (4)
Applicant Name	Fennec Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	CDER/OND/OSM/DIRM
Manufacturing Site	Berkshire Sterile Manufacturing (BSM) 480 Pleasant Street Lee, MA 01238
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: *The manufacturing of sodium thiosulfate (b) (4) in 100 mL vials consists of compounding, (b) (4) and vial filling in cGMP certified room.*

Document(s) Assessed	Date Received
Seq 0033	**06/28/2022**
Seq 0029	**03/23/2022**
Seq 0022	**05/27/2021**

List Submissions being assessed (table): Resubmissions 05/28/2021, 03/23/2022 and resubmission 06/28/2022

Highlight Key Issues from Last Cycle and Their Resolution:

(b) (4)

Resolved by Applicant's Response dated 06/28/2022 which was reviewed and was deemed adequate.

Remarks: Submitted in eCTD format. Some tables are copied from submission. The text of this review includes the MR01 review. The new information contained in this submission has been integrated into the previous review. In MR01, the Applicant responded to Agency's Information Request dated 05/01/2020 with Response to Information Request dated 05/21/2020 which was reviewed and found acceptable. The

latest Response to Agency Information Request dated 06/28/2022 is reviewed here in. Agency Information Request is italicized followed by Applicant's Response in bold within the submission.
The latest resubmission following Agency Complete Response Letter included transfer of drug product manufacturing site for [redacted] (b) (4) to BSM and update on the modules to support the sterile manufacture of drug product at new site that included [redacted] (b) (4) support the change were provided in the resubmission which upon review resulted on an IR whose Responses are reviewed here in.

Concise Description of Outstanding Issues: None

Supporting Documents: N/A

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RECOMMENDATION

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

NDA 212937
Assessment #2

Drug Product Name	PEDMARK (sodium thiosulfate)
Dosage Form	Injection
Strength	12.5 grams/100 mL
Route of Administration	for intravenous use
Rx/OTC Dispensed	Rx
Applicant	FENNEC PHARMACEUTICALS INC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
NDA resubmission	05/27/2021	CMC
Labeling	08/10/2021	DP
Quality amendment	10/19/2021	OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Kabir Shahjahan	Paresma Patel
Drug Product	Tefsit Bekele	Anamitro Banerjee
Manufacturing	Steve Hertz	Yiwei Li
Microbiology	Bernard Marasa	Julie Nemecek
Regulatory Business Process Manager	Rabiya Haider	
Application Technical Lead	Xing Wang	

Xing Wang

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 212937 resubmission is recommended for **Complete Response** based on the recommendation from the Office of Pharmaceutical Manufacturing Assessment.

The following deficiency comments should be included in the Complete Response letter:

1. ***During a recent inspection of the*** (b) (4) ***manufacturing facility for this NDA, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.***

2. ***In your complete response letter resubmission,*** (b) (4) ***previously proposed in the application from 3.2.P.3.4. When requested to confirm if you are proposing*** (b) (4) ***and if so, revise your master batch records accordingly; or to otherwise, propose*** (b) (4) ***in 3.2.P.3.4, which are supported by data in 3.2.P.2.3; you confirmed that there will be*** (b) (4) ***commercially manufactured drug product and that the commercial master batch record for the drug product*** (b) (4)***.***

(b) (4)

(b) (4)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

On August 10, 2020, FDA sent a Complete Response letter to the applicant to address the product quality and facility issues raised during the initial NDA review cycle. FDA received a class 2 resubmission on May 27, 2021

PEDMARK (sodium thiosulfate (STS) injection) is indicated for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors. The mechanism of STS protection against ototoxicity is not fully understood, but may include direct interaction between CIS and the thiol group in STS to form a non-toxic, rapidly excreted complex, scavenging reactive oxygen species, and increasing levels of endogenous antioxidants

The active ingredient STS (anhydrous) is an inorganic salt (b) (4)

The drug product is a clear and colorless sterile solution of STS provided in single (b) (4) (b) (4) 100 mL, clear glass vials that contain STS at 125 mg/mL (12.5 g STS/vial), (b) (4) and sodium hydroxide and hydrochloric acid for pH adjustment. PEDMARK is formulated for pediatric patients and is ready for use.

Based on the 18 months available data for the registration batches, the requested 24 months expiration dating period may be granted, when store at 20–25°C with temperature excursion permitted between 15°C and 30°C.

Proposed Indication(s) including Intended Patient Population	For the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non metastatic, solid tumors.
Duration of Treatment	Along with CIS treatment
Maximum Daily Dose	23 g/day

Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Adequate in previous review. Updated stability and forced degradation studies are provided in this resubmission. The proposed DS retest period of (b) (4) when (b) (4)

Drug Product: Adequate

In this resubmission, the applicant has adequately addressed three drug product information requests in the Complete Response letter issued on August 10, 2020. The assay calculation for the proposed sodium thiosulfate injection has been revised so that its potency is based on sodium thiosulfate pentahydrate content, consistent with the USP product. The proposed product, PEDMARK™ is supplied as clear, colorless sterile solution containing 125 mg sodium thiosulfate pentahydrate equivalent to 80 mg sodium thiosulfate per 1 mL in 100 mL single-dose vial. Each vial contains 12.5 grams of sodium thiosulfate pentahydrate and 250 mg boric acid (b) (4) In this resubmission, the applicant also updated the stability data to provide available 18 months data for the three registration batches stored in the inverted position and 12 months for samples stored in the upright position at long term storage conditions. The batches continued to remain within specifications. No significant chemical or physical changes at long term or accelerated storage conditions are reported in the NDA. The 18-months stability data at long-term (25 °C/60% RH) storage conditions support the storage conditions of 20–25 °C with temperature excursion permitted between 15°C and 30°C. The requested 24 months expiration date may be granted.

Labeling: Adequate

The applicant has changed the name of the proposed product to “Sodium Thiosulfate Injection” which is consistent with the USP monograph for “Sodium Thiosulfate Injection”. The assay calculation has been revised so that its potency is based on sodium thiosulfate pentahydrate content, consistent with the USP product.

Manufacturing: Inadequate

(b) (4)

(b) (4)

Microbiology: Adequate

Adequate in previous review. The resubmission included an update (b) (4) data to support the change were provided in the resubmission and upon review are deemed adequate.

C. Risk Assessment

Refer to Product Quality review #1

Application Technical Lead Name and Date:

Xing Wang, Ph.D.

Xing Wang

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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:
Refer to Product Quality review #1

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*
Refer to Product Quality review #1

2. **CONSULTS** None

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

The following information requests were sent to the applicant in the complete response letter dated August 10, 2020.

Submit draft carton can container labeling revised base on the final determination of product strength.

1. Change [redacted] (b) (4) to "12.5 grams/100 mL (125 mg/mL)" on both container labels and carton labeling to be consistent with the USP drug product monograph, where the strength is expressed as that of the pentahydrate.
2. On the container labels and carton labeling, replace [redacted] (b) (4) with "each mL contains the equivalent of sodium thiosulfate pentahydrate 125 mg (provided as sodium thiosulfate anhydrous 80 mg), 0.25 mg boric acid, NF and water for injection, USP. May contain sodium hydroxide and hydrochloric acid for pH adjustment"
3. [redacted] (b) (4)

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	PEDMARK	Adequate
Established name(s)	sodium thiosulfate injection	Adequate
Route(s) of administration	For intravenous use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	12.5 g/ 100 mL 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 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	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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)	Use immediately after withdrawing into a syringe or transferring to an empty infusion bag. If not used immediately, PEDMARK can be stored in an infusion bag for no more than 18 hours at 20°C to 22°C (68°F to 72°F). Discard unused portion.	Acceptable (b) (4)

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

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	12.5 g/100 mL	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Injection: 12.5 g/100 mL (125 mg/mL) clear, colorless 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)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	PEDMARK and sodium thiosulfate injection	Adequate
Dosage form(s) and route(s) of administration	Injection for intravenous use	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Each vial contains 12.5 grams of sodium thiosulfate pentahydrate (provided as sodium thiosulfate anhydrous 8 g) in 100 mL solution (125 mg/mL). Each mL also contains the equivalent of 125 mg of sodium thiosulfate pentahydrate (provided as sodium thiosulfate anhydrous 80 mg) and 0.25 mg boric acid. sodium hydroxide and hydrochloric acid may have been used 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.	Included (see above)	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Pharmacological/ therapeutic class	Not provided in section 11	Include the Pharmacological/ therapeutic class
Chemical name, structural formula, molecular weight	**Chemical name**: sodium thiosulfate **Structural formula**: $Na_2S_2O_3$ **Molecular weight**: 158.11 g/mol	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	It (sodium thiosulfate anhydrous) is a white to off-white crystalline solid that is soluble in water, but insoluble in alcohol. The aqueous solution has a pH ranging from 6.5 to 8.0. PEDMARK is a sterile, preservative-free, clear, colorless solution in a single-dose vial for intravenous use with a pH between 7.0 and 9.0.	Adequate
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	12.5 grams/ 100 mL	Adequate
Available units (e.g., bottles of 100 tablets)	12.5 grams/100 mL (125 mg/mL) single-dose vial, NDC 73077-010-01	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	PEDMARK (sodium thiosulfate injection) is a clear, colorless, sterile solution in flint glass single-dose vial with rubber stopper and capped with aluminum overseal supplied as: • 12.5 grams/100 mL (125 mg/mL) single-dose vial, NDC 73077-010-01	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.	Includes "single-dose"	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 at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).	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."	N/A	
Include information about child-resistant packaging	Not provided	Product is for injection and it is in glass vials sealed

1.2.5 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	Distributed by Fennec Pharmaceuticals Inc., 221 River Street, Hoboken, NJ 07030	Adequate

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling is adequate from the product quality perspective.

3.0 CARTON AND CONTAINER LABELING

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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	pedmark (sodium thiosulfate injection)	Adequate
Dosage strength	12.5 g/100 mL (125 mg/mL)	Change to 12.5 grams/100 mL (125 mg/mL) on both container and carton
Route of administration	For Intravenous use	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	100 mL	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	single-dose	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
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	Fennec Pharmaceuticals 221 River street 9th floor Hoboken, NJ 07030	Adequate
Medication Guide (if applicable)	N/A	
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	N/A	

Assessment of Carton and Container Labeling: Adequate with comments. See information requests below that will be sent to the applicant regarding CC labels.

Overall Assessment and Recommendation:

The container label and prescribing information comply with all regulatory requirements and they are recommended for approval from a CMC perspective pending revision of what are noted in the Assessor's Comments column above. The following information requests will be sent to the applicant.

1. Change "12.5g/100 mL (125 mg/mL)" to "12.5 grams/100 mL (125 mg/mL)" on both container and carton labels.

Primary Labeling Assessor Name and Date: Tefsit Bekele July 14, 2021

Secondary Assessor Name and Date Anamitro Banerjee July 14, 2021

TEFSIT BEKELE

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	212937
Assessment Cycle Number	#2
Drug Product Name/ Strength	Sodium thiosulfate (b) (4) mg/mL
Route of Administration	Intravenous (b) (4)
Applicant Name	Fennec Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	CDER/OND/OSM/DIRM
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: *The manufacturing of sodium thiosulfate (b) (4) in 100 mL vials consists of compounding, (b) (4) and vial filling in cGMP certified room.*

Document(s) Assessed	Date Received
Seq 0022	05/27/2021
Seq 0014	05/21/2020
Seq 0002	02/10/2020

List Submissions being assessed (table): Received 02/10/2020, 05/21/2020 and resubmission 05/28/2021

Highlight Key Issues from Last Cycle and Their Resolution:

1. **Container Closure Integrity Testing**
2. **Environmental Monitoring program**
3. **Equipment Sterilization.**
4. **Holding periods during drug product manufacture**
5. **(b) (4)**
6. **Endotoxin testing method validation.**
7. **Microbial challenge studies for post-reconstitution hold time.**

Resolved by Applicant's Response dated 05/21/2020 which was reviewed and was deemed adequate in the MR01 review.

Remarks: Submitted in eCTD format. Some tables are copied from submission. The text of this review includes the MR01 review. The new information contained in this submission has been integrated into the previous review. In MR01, the Applicant responded to Agency's Information Request dated 05/01/2020 with Response to Information Request dated 05/21/2020 which was reviewed and found acceptable.

Agency Information Request is italicized followed by Applicant's Response in bold within the submission
The resubmission following Agency Complete Response Letter included an update (b) (4) data to support the change were provided in the resubmission and upon review are deemed adequate.

Concise Description of Outstanding Issues: None.

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  Sodium Thiosulfate (b) (4) mg/mL solution (b) (4) (Sodium Thiosulfate (b) (4)) is a sterile solution containing 80 mg of anhydrous sodium thiosulfate per mL. The solution is provided in 100 mL clear (b) (4) glass vial with a 32 mm (b) (4) closure and a flip-off cap.

- **Drug product composition –**

Table 1: Composition of Sodium Thiosulfate (b) (4)

Ingredient	(b) (4)
Sodium Thiosulfate, anhydrous	
Boric Acid	
Sodium Hydroxide (b) (4)	
Hydrochloric Acid	
Water for Injection	

Abbreviations: NF = National Formulary; Ph. Eur.= European Pharmacopoeia; q.s. = quantum satis

- **Description of container closure system –**

Table 1: Container Closure System

Component	Description	Size	Supplier

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U.S. FOOD & DRUG ADMINISTRATION

NDA 212937
CMC LABELING ADDENDUM

Branch 1, Division of New Drug Products 1 (DNDP 1)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

Date of This Addendum:	July 31, 2020
OND Clinical Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 212937
Product Name:	PEDMARK™ (sodium thiosulfate injection)
Product Strength:	(b) (4)
Route of Administration:	IV
Applicant Name:	Fennec Pharmaceuticals, Inc.
Primary Reviewer Name:	Tefsit Bekele, Ph.D.

On February 10, 2020, Fennec Pharmaceuticals Inc has submitted a new NDA 212937 for sodium thiosulfate injection (PEDMARK™). PEDMARK™ is indicated for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors. PEDMARK™, a clear and colorless sterile solution is a ready to use formulation containing 80 mg anhydrous sodium thiosulfate per mL packaged in a 100 mL glass vial. Each vial has a total volume of 100 mL and contains 8 g of sodium thiosulfate. PEDMARK™ is administered as a 15-minute infusion, 6 hours after the completion of each cisplatin (CIS) administration.

The drug product and labeling reviews from CMC were completed and uploaded in Panorama on June 12, 2020 while the FDA and applicant were in the middle of labeling negotiations. This addendum mainly focuses on the proposed established name and product strength and supersedes the labeling review from CMC. Fennec proposed (b) (4) to be the drug product established name which does not conform to the USP monograph title (Sodium Thiosulfate Injection). During the labeling negotiation process, FDA requested that the applicant change the name to Sodium Thiosulfate Injection to comply with the USP naming policy. However, the applicant responded by stating that (b) (4) could lead to possible dosing errors due to the confusion with an already marketed Sodium Thiosulfate Injection (250 mg/mL strength marketed by Hope Pharmaceuticals indicated for treatment of acute cyanide poisoning). The strength of the commercial Sodium Thiosulfate Injection (250 mg/mL) marketed by Hope Pharmaceuticals, is expressed based on the pentahydrate form. (b) (4) The applicant's concern with dosing error is valid as there could be two USP product with the same name that have different approaches to calculate the assay/strength could lead to medication errors. However, per Section 502(g) of the FD&C Act, the applicant must conform to the current USP monograph for this product, including the strength expression. Moreover, the concern with medication errors may be avoided if the potency of the product is calculated based on the pentahydrate form as it is the case with the already marketed product.

OPPQ was consulted regarding this issue of labeling the established name and strength. During the ONDP-OPPQ internal meeting on July 10, 2020 it was determined that the established name should be changed to "Sodium Thiosulfate Injection" and the strength should be expressed as the pentahydrate form to be consistent with the USP monograph. After the ONDP-OPPQ internal meeting, the information requests 1–6 regarding the proposed name and strength were sent along with information requests 7–9.

1. Change the established name on the container labels and carton labeling from [redacted] (b) (4) to "sodium thiosulfate injection" per the USP monograph title.

2. Change [redacted] (b) (4) to "12.5 grams/100 mL (125 mg/mL)" on both container labels and carton labeling to be consistent with the USP drug product monograph, where the strength is expressed as that of the pentahydrate.

3. On the container labels and carton labeling, replace [redacted] (b) (4) with "each mL contains the equivalent of sodium thiosulfate pentahydrate 125 mg (provided as sodium thiosulfate anhydrous 80 mg), 0.25 mg boric acid, NF and water for injection, USP. May contain sodium hydroxide and hydrochloric acid for pH adjustment"

4. Test PEDMARK registration batches in accordance to the USP monograph for Sodium Thiosulfate Injection. You may use an alternative test method for assay, however, the USP method will be considered the regulatory method. Refer to USP General Notices and Requirements: *6.30 Alternative and Harmonized Methods and Procedure*s for more details.

5. Submit a new assay test method that is intended for commercial use. You may revise the calculations for the current non-compendial ion chromatography assay method so that the potency of the drug product is calculated based on the sodium thiosulfate pentahydrate form.

6. If you plan to use the currently proposed commercial assay test method which is non-compendial, provide comparative data to show the method produces comparable results to the compendial test method. Per the USP monograph, the assay must be calculated based on sodium thiosulfate pentahydrate.

7. Include "Sterile" on both the container and carton labels.

8. Include a complete full address for Fennec Pharmaceuticals.

9. Replace the storage condition with "Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F)" on the carton and container label.

The applicant requested a teleconference with the FDA to discuss the product quality information requests regarding [redacted] (b) (4) the established name and the request for testing PEDMARK registration batches in accordance to the USP monograph for Sodium Thiosulfate Injection. During the teleconference held with the applicant on July 23, 2020, the FDA reiterated that the proposed drug product must conform to the USP monograph and indicated that the applicant should work with the Division of Oncology 2 to recalculate the dosing regimen described in the USPI based on the recalculated strength per USP monograph.

The applicant was asked to work with the OND to convert all the clinical information in the relevant sections of the USPI from the anhydrous form to the equivalent amounts of pentahydrate sodium thiosulfate. The applicant stated that they are in agreement to change the name to "Sodium Thiosulfate Injection" [redacted (b) (4)] The applicant also indicated that the proposed product is not for the same indication as the currently approved product from Hope Pharmaceuticals which is for the treatment of acute cyanide poisoning. The applicant indicated that changing the strength of the drug product as indicated in the USP monograph may lead to confusion and medication errors.

The Agency indicated that it cannot control off-label use of the products after approval. As a result, the Hope product and the proposed product could be used interchangeably. In such a scenario, differences in strength calculations (anhydrous vs. pentahydrate) may cause serious medication errors. The applicant suggested that the FDA and the applicant work together to modify the current USP monograph. The FDA indicated that such an effort would be impractical considering the widespread use of the product that has been on the market for several years to treat cyanide poisoning. The applicant indicated that they will consider Agency's comments in their response to the FDA's information request comments.

On July 27, 2020 the applicant submitted a formal written response to the information requests sent in the prior week. Fennec formally agreed to change the name so that it is consistent to the USP monograph title however the applicant's position on the strength has not changed since the teleconference. They indicated that the strength of their product should be [redacted (b) (4)] based on the following arguments:

- Pentahydrate was never used for this product, and using this form for the calculation of the strength is misleading and may cause medical errors
- Sodium thiosulfate active concentration is consistent with the current USP policy.
- Seek FDA input to change the USP monograph

The applicant did not provide a compelling reason to keep the [redacted (b) (4)] strength for the proposed product and FDA's position has not changed as the applicant should follow the USP monograph. The major concern FDA has is that the same sodium thiosulfate injection product for two different indications using two different approaches to calculate the strength could lead to medication errors. Changing the USP monographs as the applicant recommended at this stage is difficult as it will cause a lot of confusion for an already established product.

CONCLUSION: Not Acceptable.

The applicant has addressed the information requests # 1, 7–9 and the corresponding responses were found acceptable. The OPQ does not agree with the applicant response regarding the calculation of the strength of the proposed product. The following comments should be conveyed to the applicant:

1. Change [redacted] (b) (4) to "12.5 grams/100 mL (125 mg/mL)" on both container and carton labeling to be consistent with the USP drug product monograph, where the strength is expressed as that of the pentahydrate. The Agency does not agree with the justification provided in your response dated July 27, 2020 to continue calculating the strength [redacted] (b) (4) as it does not comply with Section 502(g) of the FD&C Act.

2. On the container and carton labeling, replace [redacted] (b) (4) with "each mL contains the equivalent of sodium thiosulfate pentahydrate 125 mg (provided as sodium thiosulfate anhydrous 80 mg), 0.25 mg boric acid, NF and water for injection, USP. May contain sodium hydroxide and hydrochloric acid for pH adjustment".

3. Update relevant sections of the USPI to reflect the change in strength to 12.5 grams/100 mL (125 mg/mL)

4. Test PEDMARK registration batches in accordance to the USP monograph for Sodium Thiosulfate Injection. You may use an alternative test method for assay, however, the USP method will be considered the regulatory method. Refer to USP General Notices and Requirements: *6.30 Alternative and Harmonized Methods and Procedure*s for more details.

5. Submit a new assay test method that is intended for commercial use. You may revise the calculations for the current non-compendial ion chromatography assay method so that the potency of the drug product is calculated based on the sodium thiosulfate pentahydrate form.

6. If you plan to use the currently proposed commercial assay test method which is non-compendial, provide comparative data to show the method produces comparable results to the compendial test method. Per the USP monograph, the assay must be calculated based on sodium thiosulfate pentahydrate.

Primary Labeling Assessor: Tefsit Bekele PhD, OPQ/ONDP/DNDPI/NDPBI, Review chemist 7/31/2020

Secondary Labeling Assessor: Anamitro Banerjee PhD, OPQ/ONDP/DNDPI/NDPBI, Branch Chief 7/31/2020

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/

TEFSIT BEKELE
08/03/2020 07:43:44 AM

ANAMITRO BANERJEE
08/03/2020 09:18:05 AM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 212937
Assessment #1

Drug Product Name	PEDMARK (sodium thiosulfate)
Dosage Form	Injection
Strength	(b) (4)
Route of Administration	for intravenous use
Rx/OTC Dispensed	Rx
Applicant	FENNEC PHARMACEUTICALS INC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	02/10/2020	CMC
Quality Amendment	03/20/2020	OPMA
Labeling Amendment	04/15/2020	DP
Quality Amendment	05/21/2020	DP, OPMA, Microbiology
Quality Amendment	06/25/2020	OPMA
Labeling Amendment	07/27/2020	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Kabir Shahjahan	Ali Al Hakim
Drug Product	Tefsit Bekele	Anamitro Banerjee
Manufacturing	Steve Hertz	David Anderson
Microbiology	Bernard Marasa	Neal Sweeney
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xing Wang	

Xing Wang

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 212937, Sodium Thiosulfate Injection, is recommended for **Complete Response** based on the "**withhold**" recommendation from the Office of Pharmaceutical Manufacturing Assessment. Specifically, at the conclusion of the recent (b) (4) facilities inspection, the initial field recommendation was to withhold. OPMA evaluated the inspection outcome and concurred with the recommendation to withhold due to a lack of capacity to manufacture the drug product.

The following deficiency comments should be included in the action letter:

(b) (4) ***manufacturing facility for this NDA, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.***

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

PEDMARK (sodium thiosulfate (STS) injection) is indicated for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors. The mechanism of STS protection against ototoxicity is not fully understood, but may include direct interaction between CIS and the thiol group in STS to form a non-toxic, rapidly excreted complex, scavenging reactive oxygen species, and increasing levels of endogenous antioxidants

The active ingredient STS (anhydrous) is an inorganic salt (b) (4)

The drug product is a clear and colorless sterile solution of STS provided in single (b) (4) (b) (4) 100 mL, clear glass vials that contain STS (b) (4) water for injection, boric acid (b) (4) sodium hydroxide and hydrochloric acid for pH adjustment. PEDMARK is formulated for pediatric patients and is ready for use. There are on-going labeling discussions regarding proper product

strength expression per related USP monograph (see Labeling section). The issue is unlikely to be resolved in this round of review.

Based on the 9 months available data for the registration batches, the requested 18 months expiration dating period may be granted, when store at 20–25°C with temperature excursion permitted between 15°C and 30°C.

Proposed Indication(s) including Intended Patient Population	For the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non metastatic, solid tumors.
Duration of Treatment	Along with CIS treatment
Maximum Daily Dose	23 g/day
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Drug substance (DS) sodium thiosulfate (STS) is an inorganic salt. (b) (4) [redacted] The source of generation of all potential impurities is well understood and demonstrated with test results of many batches of the drug substance. No impurity limit exceeds the USP monograph, justified impurity limit, and ICH Q3A qualification threshold. Adequate justification based on risk assessment for elemental impurities contamination was completed, and the inclusion of elemental impurities testing is not considered necessary for this application. Adequate assessment for mutagenic impurities was carried out by evaluating potential impurities arising from the DS synthesis. However, the applicant noted that a complete assessment of potential genotoxic impurities is not applicable per ICH M7 and ICH S9, considering the indication to be treated. The batch analyses data of thirteen batches of DS conform to the proposed DS specification. Stability data on the three registration batches supports a retest period of [redacted] (b) (4) for sodium thiosulfate per ICH Q1E (R2).

Drug Product: Adequate

PEDMARK™ (sodium thiosulfate injection) is supplied as clear, colorless sterile solution containing 80 mg anhydrous sodium thiosulfate per 1 mL in 100 mL single-dose vial. Each vial contains 8 grams of anhydrous

sodium thiosulfate and (b) (4) mg boric acid (b) (4) The formulation may contain sodium hydroxide and hydrochloric acid for pH adjustment (b) (4) There is no preservative in the formulation and after pH adjustment, (b) (4) Sodium thiosulfate injection manufactured using pentahydrate sodium thiosulfate drug substance is currently marketed for treatment of cyanide poisoning. Phase III clinical studies have been conducted using commercial supply (250 mg/mL sodium thiosulfate) that was later discontinued. Fennec manufactured similar sodium thiosulfate ready for-use formulation (b) (4) . The clinical batches after 1:1 dilution with water are equivalent to the registration batches. Stability studies have been conducted on three registration batches stored in upright and inverted orientations. Three months and six months stability data at long term are initially submitted for the upright and inverted positions respectively. The applicant later updated the stability section and 9 months data for the inverted position at long term became available. Six months stability data are also available for both vial orientations under accelerated storage conditions. No significant chemical or physical changes at long term or accelerated storage conditions are reported in the NDA. The 9-months stability studies at long-term (25 °C/60% RH) storage conditions supports the storage conditions of 20–25 °C with temperature excursion permitted between 15 °C and 30 °C. Based on the 9 months available data for the registration batches, the requested 18 months expiration date may be granted.

Labeling: Inadequate

The applicant must change the name of the proposed product from (b) (4) to "Sodium Thiosulfate Injection" as the USP does not allow the use of terms such as (b) (4)" The USP has a monograph for "Sodium Thiosulfate Injection", so the applicant must conform to this monograph. This monograph pre-dates the salt policy and expresses the strength as pentahydrate. The pentahydrate was never used in the manufacture/composition of the proposed product. From FDA perspective, the proposed product strength should be 125 mg/mL (expressed in terms of pentahydrate), (b) (4) avoid expression of strength in two different ways for a product with the same name – a potential for medication errors. (b) (4) The discussion is still on-going, not likely to be resolved in this round of review.

Manufacturing: Inadequate

(b) (4)

Microbiology: Adequate

The manufacturing of sodium thiosulfate (b) (4) consists of compounding, (b) (4) and vial filling in cGMP certified room. Applicant responded to Agency's Information Request dated 05/01/2020 with Response to Information Request dated 05/21/2020, which was reviewed and found acceptable.

The following issues were resolved.

1. Container Closure Integrity Testing
2. Environmental Monitoring program
3. Equipment Sterilization.
4. Holding periods during drug product manufacture
5. (b) (4)
6. Endotoxin testing method validation.
7. Microbial challenge studies for post-reconstitution hold time.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	Release and stability specs; Facility inspection	**Not acceptable per Pre-Approval Inspection**	

Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M	Release and stability specs	Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	
Appearance (Color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Particulate matter	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Release and stability specs	Acceptable	
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
pH- (High)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	

Application Technical Lead Name and Date:

Xing Wang

Xing Wang

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U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Adequate	06/02/2020	MAPP 5015.5 (Rev.1)
	III			Adequate	06/02/2020	
	III			Adequate	06/02/2020	

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

Document	Application Number	Description
IND	72877	Drug development

2. CONSULTS None

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	PEDMARK	Adequate
Established name(s)	(b) (4)	Change to: (Sodium thiosulfate injection)
Route(s) of administration	For intravenous use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	
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.	(b) (4)	Change to: Single-dose

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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)	(b) (4) [redacted]	Acceptable. (b) (4) [redacted]

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

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	(b) (4)	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4)	
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.	(b) (4)	Change to: Single-dose vial

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	PEDMARK and sodium thiosulfate (b) (4) injection	Change to: PEDMARK and (sodium thiosulfate injection)
Dosage form(s) and route(s) of administration	Injection for intravenous use	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4)	Change to: (b) (4) and 0.25 mg boric acid. Sodium hydroxide and hydrochloric acid may have been used for pH adjustment.
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.	Included (see above)	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Pharmacological/ therapeutic class	Reducing agent	Adequate
Chemical name, structural formula, molecular weight	**Chemical name**: sodium thiosulfate **Structural formula**: $Na_2S_2O_3$ **Molecular weight**: 158.11 g/mol	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	It is a white to off-white crystalline solid that is soluble in water, but insoluble in alcohol. The aqueous solution (b) (4) [redacted] a pH ranging from 6.5 to 8.0. (b) (4) [redacted]	Change the second paragraph to: PEDMARK is a sterile, preservative-free, clear, colorless solution in a single-dose vial for intravenous use with a pH between 7.0 and 9.0.
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	(b) (4)	Adequate
Available units (e.g., bottles of 100 tablets)	PEDMARK contains sodium thiosulfate, (b) (4)	Change to: (b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Change to: PEDMARK (sodium thiosulfate injection) is a clear, colorless, sterile solution in flint glass single-dose vial with rubber stopper and capped with aluminum overseal
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.	Not provided	"Single-dose" has been added

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	N/A	

form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4) stored at (b) (4) between 15°C and 30°C (59°F and 86°F).	Change to: Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F)
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."	N/A	
Include information about child-resistant packaging	Not provided	Product is for injection and it is in glass vials sealed

1.2.5 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	Distributed by Fennec Pharmaceuticals Inc., (b) (4)	Applicant will be requested to provide a complete address

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling is adequate from the product quality perspective.

3.0 CARTON AND CONTAINER LABELING

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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	pedmark (sodium thiosulfate (b) (4) injection)	Change to: pedmark (sodium thiosulfate injection)
Dosage strength	(b) (4)	
Route of administration	For Intravenous use	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	(b) (4)	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	Change to: Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	(b) (4)	Change to: 1 single-dose vial (on the container label) And single-dose vial (on the container label)
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
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	Fennec Pharmaceuticals (b) (4)	Full address need to be included
Medication Guide (if applicable)	N/A	
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	N/A	

Assessment of Carton and Container Labeling: Adequate with comments. See information requests below.

Overall Assessment and Recommendation:

The container label and prescribing information comply with all regulatory requirements and they are recommended for approval from a CMC perspective pending revision of what are noted in the Assessor's Comments column above. The following information requests will be sent to the applicant. Note that some of the comments noted above were communicated to applicant by the DMEPA reviewer.

1. Include “Sterile” on both the container and carton labels.
2. Change [redacted] (b) (4) on both container and carton labels.
3. Change the name “pedmark [redacted] (b) (4) to “pedmark (sodium thiosulfate injection)”.
4. Include a complete full address for Fennec Pharmaceuticals.
5. Replace the storage condition with “Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F)” on the carton and container label
6. Replace [redacted] (b) (4) 0.25 mg boric acid, NF and water for injection, USP. May contain sodium hydroxide and hydrochloric acid for pH adjustment” on the container/carton label.

Primary Labeling Assessor Name and Date: Tefsit Bekele June 02, 2020

Secondary Assessor Name and Date Anamitro Banerjee

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Banerjee

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	212937
Assessment Cycle Number	#1
Drug Product Name/ Strength	Sodium thiosulfate (b) (4) mg/mL
Route of Administration	Intravenous infusion
Applicant Name	Fennec Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: *The manufacturing of sodium thiosulfate (b) (4) in 100 mL vials consists of compounding, (b) (4) and vial filling in cGMP certified room.*

Document(s) Assessed	Date Received
Seq 0014	**05/21/2020**
Seq 0002	**02/10/2020**

List Submissions being assessed (table): Received 02/10/2020, 05/21/2020

Highlight Key Issues from Last Cycle and Their Resolution:

1. **Container Closure Integrity Testing**
2. **Environmental Monitoring program**
3. **Equipment Sterilization.**
4. **Holding periods during drug product manufacture**
5. (b) (4)
6. **Endotoxin testing method validation.**
7. **Microbial challenge studies for post-reconstitution hold time.**

Resolved by Applicant's Response dated 05/21/2020 which was reviewed and was deemed adequate.

Remarks: Submitted in eCTD format. Some tables are copied from submission. Applicant responded to Agency's Information Request dated 05/01/2020 with Response to Information Request dated 05/21/2020 which was reviewed and found acceptable. Agency Information Request is italicized followed by Applicant's Response in bold within the submission.

Concise Description of Outstanding Issues: None.

8.

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  Sodium Thiosulfate (b) (4) mg/mL solution (b) (4) (Sodium Thiosulfate (b) (4)) is a sterile solution containing 80 mg of anhydrous sodium thiosulfate per mL. The solution is provided in 100 mL clear (b) (4) glass vial with a 32 mm (b) (4) closure and a flip-off cap.

- **Drug product composition –**

Table 1: Composition of Sodium Thiosulfate (b) (4)

Ingredient	(b) (4)
Sodium Thiosulfate, anhydrous	
Boric Acid	
Sodium Hydroxide (b) (4)	
Hydrochloric Acid	
Water for Injection	

Abbreviations: NF = National Formulary; Ph. Eur.= European Pharmacopoeia; q.s. = quantum satis

- **Description of container closure system –**

(b) (4)

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/s/

XING WANG
07/28/2020 12:07:50 PM