CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208969Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA Executive Summary NDA 208969 Assessment 2

1. Application/Product Information

NDA Number.	208969
Applicant Name	Amphastar Pharmaceuticals, Inc.
Drug Product Name	Naloxone HCl Nasal Spray (N002)
Dosage Form.	Spray
Proposed Strength(s)	4 mg/0.25 mL (16 mg/mL)
Route of Administration	Nasal
Maximum Daily Dose	8 mg
Rx/OTC Dispensed	Rx
Proposed Indication	(b) (4)
Drug Product Description	Clear, colorless solution in a prefilled syringe
Co-packaged product information	N/A

Device information:	(b) (4)		
Storage Temperature/ Conditions	store at controlled room temperature, 68°F - 77°C (20°C - 25°C)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Gaetan Ladouceur
	Drug Product/ Labeling	Mariappan Chelliah	Julia Pinto
	Manufacturing	Qiang Han	Kamal Tiwari
	Biopharmaceutics	N/A	N/A
	Microbiology	George K. Arhin	Elizabeth Bearr
	Other (specify):	N/A	N/A
	RBPM	Anika Lalmansingh	
	ATL	Valerie Amspacher	
Consults	Kyran Gibson (CDRH)		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed shelf-life of 24 months when stored at 20°C to 25°C with excursions permitted between 39°F to 104°F (4°C to 40°C) is acceptable.

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

This resubmission is a response to a CR issued 17 Feb 2017. In this resubmission the applicant has provided a completely new formulation and device. After review, all CMC disciplines recommend approval.

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:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

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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	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	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.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	

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

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	

For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	N/A	
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 type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For 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	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	N/A	
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.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	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."*	Adequate	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

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

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

Copy of the container label from SN0059:

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

3.2 Carton Labeling

Copy of the carton label from SN0059:

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Inadequate	Salt equivalency statement is currently missing. The labeling will be edited to meet this requirement.
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
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, and these products require a "Not for direct infusion" statement.	N/A	The labeling will be edited to replace "(b) (4)" with "unit-dose"
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	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***

The carton and container labels will be edited to change packaging term (from "(b) (4) to "unit-dose") and to include salt equivalency statement.

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan V Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

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Julia Pinto

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U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	
NDA Number	208969-ORIG-1-RESUB-50
Assessment Cycle Number	2
Drug Product Name / Strength	Naloxone Hydrochloride Nasal Spray, 4 mg/0.25 mL
Route of Administration	Nasal
Applicant Name	Amphastar Pharmaceuticals, Inc.
Manufacturing Site	International Medication Systems, Ltd. (IMS) 1886 Santa Anita Avenue South El Monte, CA 91733 FEI: 2016148 DUNS No.: 055750020
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme: N/A

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: N/A

Assessment Summary: The submission **is recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed:

Submit	Received	Review Request	Assigned to Reviewer
September 7, 2022 (eCTD Sequence #0049)	September 7, 2022	N/A	September 20, 2022
December 2, 2022 (eCTD Sequence #0054)*	December 2, 2022	N/A	December 2, 2022

*December 2, 2022 submission is response submission to Agency's November 18, 2022 IR letter/e-mail.

Submission History:

Submit	Microbiology Review #	Review date
April 19, 2016	1	August 30, 2016
August 6, 2016		

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

Concise Description of Outstanding Issues:

Supporting Documents:

- 208969/ Original NDA submission, submit date: 04/19/2016. Reviewed in Microbiology N208969MR01.docx dated 08/30/2016. Adequate

Remarks: The subject September 7, 2022 NDA amendment submission (eCTD Sequence #0049) was originally intended to provide responses to address deficiencies communicate to the NDA sponsor in a Complete Response (CR) Letter dated February 17, 2017 by Division of Anesthesia, Analgesia and Addiction Products. However, following the receipt of the CR Letter and additional communications with the Agency and advice provided in these subsequent communications, the NDA submitting this amendment (NDA 208969, Sequence 0049) to provide for major improvements/changes made to the drug product. The proposed changes are

- (b) (4) **4 mg/0.25 mL (16 mg/mL)**.
- The filling volume is (b) (4) 0.25 mL.
- The Nasal Injector is (b) (4) pre-assembled, ready to use.

The amendment also addresses the Division of Anesthesia deficiencies in the February 17, 2017 CR letter.

Select Number of Approved Comparability Protocols: 0

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  The original NDA submission provided for the manufacture of a (b) (4) ((b) (4) drug product. The drug product in the subject NDA is a 4 mg/0.25 mL.

- **Drug product composition** –

Ingredient	Quantity per mL (mg/mL)	Quantity per vial (mg/0.25 mL)	Function
Naloxone HCl Dihydrate, USP	(b) (4)		Active Pharmaceutical Ingredient
Sodium Chloride, USP			(b) (4)
Sodium Hydroxide, NF	q.s.	q.s.	pH Adjuster
Water for Injection, USP	(b) (4)		(b) (4)
(b) (4)			

Note to Reviewer: (b) (4) drug product strength from (b) (4) **in the** original NDA submission to the proposed **4 mg/0.25 mL** changes/ (b) (4) the API concentration from (b) (4) to 16 mg/mL. With this change, Sodium Hydroxide NF is used as the excipient for pH adjustment instead of (b) (4)

- **Description of container closure system –**
The vial and stopper for the proposed 4 mg/0.25 mL drug product are the same as the container/closure system for the original (b) (4) drug product. The primary CCS consists of a 3 mL (b) (4) glass container with luer-lock tip of the injector attached with an intranasal tip.

Component	Description	Manufacturer/Supplier
Container	3 mL (b) (4) glass vial	(b) (4)
Closure	2 mL (b) (4) gray stopper	

Additional Information and Analysis: The drug product kit includes a Nasal Injector to be attached to the vial holder to provide a ready-to-use Nasal Spray Unit. (b) (4) the Nasal Injector for the 4 mg/0.25 mL drug product drug product is (b) (4) pre-assembled, ready to use.

Schematic Drawing for Nasal Spray Unit
(3.2.P.2 page 4 of 17)

(b) (4)

(b) (4)

Reviewer's Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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George Arhin

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Elizabeth Bearr

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Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 2/16/2023 04:43:08PM
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/s/

VALERIE R AMSPACHER
02/16/2023 04:49:55 PM

Recommendation: Approval pending facilities

NDA 208969
Review #1

Drug Name/Dosage Form	Naloxone Hydrochloride Nasal Spray()/Spray
Strength	(b) (4)
Route of Administration	Nasal
Rx/OTC Dispensed	Rx
Applicant	Amphastar Pharmaceuticals, Inc.
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	OPQ/ONDP/DNDPAPI/BII
Drug Product	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV
Process	Edwin Jao	OPQ/OPF/DPAIII/BVII
Microbiology	Nutan Mytle	OPQ/OPF/DMA/BII
Facility	Christina Capacci-Daniel	OPQ/OPF/DIA/BII
Biopharmaceutics		
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Ciby Abraham	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Approve	8/9/16	
	Type III			Approve	1/18/17	
	Type III			Approve	1/18/17	
	Type III			Approve	1/18/17	
	other			Approve	1/18/17	
	Type III			Approve	12/8/16	
	Type III			Approve	1/18/17	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	124672	Intranasal Naloxone for treatment of opioid overdose
Pre-IND	124672	Meeting Minutes
ANDA	072076	Reference to CMC information

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH OC	Pending			

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug substance, drug product, microbiology, and process, CMC recommends approval of (b) (4) Nasal Spray (b) (4) pending the overall recommendation from facilities.

II. Summary of Quality Assessments

A. Product Overview

The proposed indication of (b) (4) Nasal Spray is (b) (4) The product comprises of (b) (4) Naloxone HCl solution in a glass vial (b) (4). (b) (4) nasal spray will be supplied in a box containing two single dose nasal spray devices, (b) (4)

The drug substance, Naloxone HCl is manufactured by (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed 8/9/2016). Naloxone HCl is a white to off-white powder with a molecular weight of 399.87 g/mol. Additional information on the production of Naloxone HCl, method of manufacturing, characterization, specification, and stability are found in DMF# (b) (4) A retest period of (b) (4) months was established for Naloxone HCl dihydrate when stored at (b) (4)

B. Special Product Quality Labeling Recommendations (NDA only) –N/A

C. Final Risk Assessment (see Attachment)

D. From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-

Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.
Primary Quality Review

Application Technical Lead Name and Date:

_____

Ciby J. Abraham, Ph.D.
Acting Quality Assessment Lead
OPQ/ONDP/DIVII/Branch IV

Recommendation: Complete Response

NDA 208969
Review #2

Drug Name/Dosage Form	Naloxone Hydrochloride Nasal Spray()/Spray
Strength	(b) (4)
Route of Administration	Nasal
Rx/OTC Dispensed	Rx
Applicant	Amphastar Pharmaceuticals, Inc.
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	OPQ/ONDP/DNDPAPI/BII
Drug Product	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV
Process	Edwin Jao	OPQ/OPF/DPAIII/BVII
Microbiology	Nutan Mytle	OPQ/OPF/DMA/BII
Facility	Christina Capacci-Daniel	OPQ/OPF/DIA/BII
Biopharmaceutics		
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Ciby Abraham	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments

(b) (4)	Type II	(b) (4)	Approve	8/9/16	
	Type III		Approve	1/18/17	
	Type III		Approve	1/18/17	
	Type III		Approve	1/18/17	
	other		Approve	1/18/17	
	Type III		Approve	12/8/16	
	Type III		Approve	1/18/17	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	124672	Intranasal Naloxone for treatment of opioid overdose
Pre-IND	124672	Meeting Minutes
ANDA	072076	Reference to CMC information

Executive Summary

I. Recommendations and Conclusion on Approvability

This memo is to update the overall recommendation from CMC on 1/19/2017, which stated "Based on the recommendations from drug substance, drug product, microbiology, and process, CMC recommends approval of (b) (4) Nasal Spray (b) (4) pending the overall recommendation from facilities." On 2/16/2017, facilities provided an overall recommendation of withhold. Therefore, CMC recommends a complete response for NDA 208969.

Deficiency from Facilities:

1. During a recent inspection of the International Medication Systems Limited (FEI 2016148) manufacturing facility for this application, our field investigator conveyed device (21 CFR 820) deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

In Dr. Valerie Amspacher's review of the extractables/leachables, she stated "Overall DP Recommendation: Approvable pending resolution of outstanding deficiencies listed below.

Concise Description Outstanding Issues Remaining:
Since this application will be a complete response due to inspection issues, the following CMC comment is included in the Complete Response letter:
In module 3.2.P.7.4, a report titled, "Addendum to Naloxone HCl Intranasal (N002) Extractable and Leachable Assessment," states, "Furthermore, non-volatile extractables and leachables testing were examined using (b) (4) instrumentation. The (b) (4) method is referenced from (b) (4) Technical Report and used to study non-volatile extractables and leachables. No extraneous peaks were detected analyzed with specified (b) (4) method." This does not provide confidence in the firm's ability to adequately monitor non-volatile extractables/leachables. Clarify which extractables/leachables standards were used when running the (b) (4) samples. Provide validation information on the (b) (4) method showing it is capable of detecting the likely extractables/leachables present. (b) (4) This does not provide confidence in the firm's ability to adequately monitor extractables/leachables. (b) (4)

After internal discussions, the drug product group recommends approval and will send the following extractable/leachable comments to the applicant as additional comments and not as deficiencies.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. The description of the non-volatile leachables testing in the extractables and leachables report is inadequate to assure accurate monitoring of non-volatile extractables/leachables. Clarify which extractables/leachables standards were used when running the (b) (4) samples. Provide validation information on the (b) (4) method showing it is capable of detecting the likely extractables/leachables present.

2. There is an unexplained inconsistency in the results of the extractions studies using similar conditions in the assessment of extractables and leachables. (b) (4)

Application Technical Lead Name and Date:

_____

Ciby J. Abraham, Ph.D.
Acting Quality Assessment Lead
OPQ/ONDP/DIVII/Branch IV

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Product Quality Microbiology Review

30 August 2016

NDA: 208969

Drug Product Name

Proprietary: (b) (4) (initially proposed)

Non-proprietary: Naloxone Hydrochloride Nasal Spray

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
4/19/2016	4/19/2016	N/A	4/28/2016
8/6/2016*	8/8/2016	N/A	8/8/2016

*IR Response

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
N/A	N/A	N/A

Applicant/Sponsor

Name: Amphastar Pharmaceuticals, Inc.

Address: 11570 6th Street, Rancho Cucamonga, CA, 91730

Representative: Gisela Sharp, Senior Manager, Regulatory Affairs

Telephone: 909-980-9484, ext. 2016

Fax: 1-909-908-6422

Name of Reviewer: Nutan Mytle, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: Initial marketing of (b) (4) drug product.

3. MANUFACTURING SITE:
(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Nasal spray, (b) (4) (b) (4) single dose units

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Indicated for - (b) (4) opioid over-dosage.

B. SUPPORTING/RELATED DOCUMENTS: ANDA 072076

C. REMARKS: This is an eCTD submission. Agency sent an IR request letter dated 6/29/2016. IR response letter was received on 8/8/2016. This review also includes the IR responses.
(b) (4)

Filename: N208969MR01.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

(b) (4)

B. Brief Description of Microbiology Deficiencies –

None

C. Contains Potential Precedent Decision(s) - ☐ Yes ☒ No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
(b) (4)							

(b) (4)

B. Final Risk Assessment - No microbiology deficiencies were identified. (b) (4)

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Nutan Mytle, Ph.D.
Microbiology Secondary Reviewer/ Neal J. Sweeney, Ph.D.

C. CC Block
cc: Field Copy

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**
  Nasal spray, (b) (4)

- **Drug product composition –**

Ingredients	Function	Quantity/mL
Naxolone HCl Dihydrate USP*	API	(b) (4)

(b) (4)

Description of container closure system – (QOS 2/38)

Component	(b) (4)
Description	
Manufacturer	
IMS Part No.	

(b) (4)

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

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Neal Sweeney

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Nutan Mytle

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Steven Kinsley

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Ciby Abraham

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