CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208969Orig1s000

OTHER REVIEW(S)

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	3/6/2023		
To:	Anika Lalmansingh		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Other
From	Kyran Gibson OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA 208969, Naloxone Nasal Spray ICC2200783/ICC2200784 00871638/00871642		
Recommendation	**Mid-Cycle Recommendation Date: 12/9/2022** ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☑ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 3/6/2023 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Kyran R. Gibson -S Digitally signed by Kyran R. Gibson -S Date: 2023.03.07 16:05:33 -05'00'		

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 208969
Sponsor	Amphastar Pharmaceuticals
Drug/Biologic	Naloxone Nasal Spray
Indications for Use	(b) (4)
Device Constituent	Nasal Spray
Related Files	ICC2000107

Review Team		
Lead Device Reviewer	*Kyran Gibson*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			
Human Factors Validation			X	
Facilities & Quality Systems	X			

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

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3. PURPOSE/BACKGROUND

3.1. Scope

Amphastar Pharmaceuticals is requesting approval of Naloxone Nasal Spray. The device constituent of the combination product is a Nasal Spray.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

This is a resubmission for NDA 208969 naloxone nasal spray 4mg/0.25 mL. The CR was issued in 2017 (attached to this request). There were deficiencies related to the device design.

This review will cover the following review areas:

Facilities, Device Description, Labeling, Design Control, Risk Analysis, Design Verification, Clinical Validation, Quality Systems

This review will not cover the following review areas:

Human Factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

This is a resubmission for Naloxone Nasal Spray after issuance of a CR in 2017 based on the human factors study, issues with device design, and safety concerns for the proposed volume (b) (4) in very young pediatric patients. The Sponsor submitted a meeting request in 2020 requesting Agency feedback regarding changes to device design, stability, and reliability.

3.2.1. Related Files

ICC2000107

3.3. Indications for Use

Combination Product	Indications for Use
Naloxone Nasal Spray	(b) (4)
Nasal Spray	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0049	1.1 Forms 1.2 Cover Letters 1.11 Information Not Covered Under Modules 2 to 5 1.14 Labeling 2.3 Quality Overall Summary 3.2.P Drug Product

	3.2.R Regional Information 5.3 Clinical Study Reports
0057	1.11 Information Not Covered Under Modules 2 to 5 3.2.P Drug Product 3.2.R Regional Information
0062	1.11.1 Quality Information Amendment 3.2.P.5 Control of Drug Product 3.2.P.8 Stability 3.2.R Regional Information
0067	1.11.1 Quality Information Amendment 3.2.R Regional Information
0069	1.11.1 Quality Information Amendment 3.2.R Regional Information
0070	1.11.1 Quality Information Amendment 3.2.R Regional Information
0071	1.11.1 Quality Information Amendment 3.2.R Regional Information

4. DEVICE DESCRIPTION

4.1. Device Description

The proposed combination product is the emergency-use Naloxone Nasal Spray 4mg/0.25ml (16mg/ml). The product is single use, pre-assembled, and ready-to-use nasal spray device.

The final finished device consists of a 3ml (b) (4) Glass Vial, a 2ml (b) (4) Stopper, and the N002 Nasal Injector as outlined in **Figure 1**. The N002 Nasal Injector molded components include the Intranasal Tip, Nasal Tip Insert, 3ml Nasal Barrel, Nasal Cannula Centering Guide, and 3ml Vial Holder shown in **Figure 3**.

	Medication Container (Primary)	Rubber Stopper (Primary)	N002 Nasal Injector (Secondary)
Description	3 mL (b) (4) glass container	2 mL (b) (4) (b) (4) gray stopper	Each N002 nasal Injector is preassembled with a medication filled, stoppered vial attaching to a vial holder to provide a ready-to-use N002 Nasal Spray Unit
Manufacturer	(b) (4)		International Medication Systems, Limited (IMS)
IMS' Part No.	(b) (4)		

Figure 1. Components of the Naloxone Nasal Spray 4mg/0.25ml (16mg/ml)

Table 1. Materials of molded components of the N002 Nasal Injector

Component	Material
Intranasal Tip	(b) (4)
Nasal Tip Insert	
3ml Nasal Barrel	
Nasal Cannula Centering Guide	
3ml Vial Holder	

*All plastic components are molded in-house (IMS).

During intranasal delivery, the user presses the vial holder (green plunger) until it stops to give the entire dose. When the plunger is pressed, the internal cannula of the nasal injector pierces the vial stopper to form a continuous fluid pathway from the vial through the intranasal tip for delivery. The vial holder allows a larger surface area for ease of use and ensures the vial becomes locked into the injector after use.

The submission is requesting a 24 month expiration dating for the proposed combination product. The product will be supplied as one (1) nasal spray unit and one (1) Instructions for Use per blister with two (2) blisters and one (1) package insert available in each carton. The product should be stored between 20 – 25C (68 – 77F) with excursions between 4C – 40C (39F – 104F) without freezing or exposure to light.

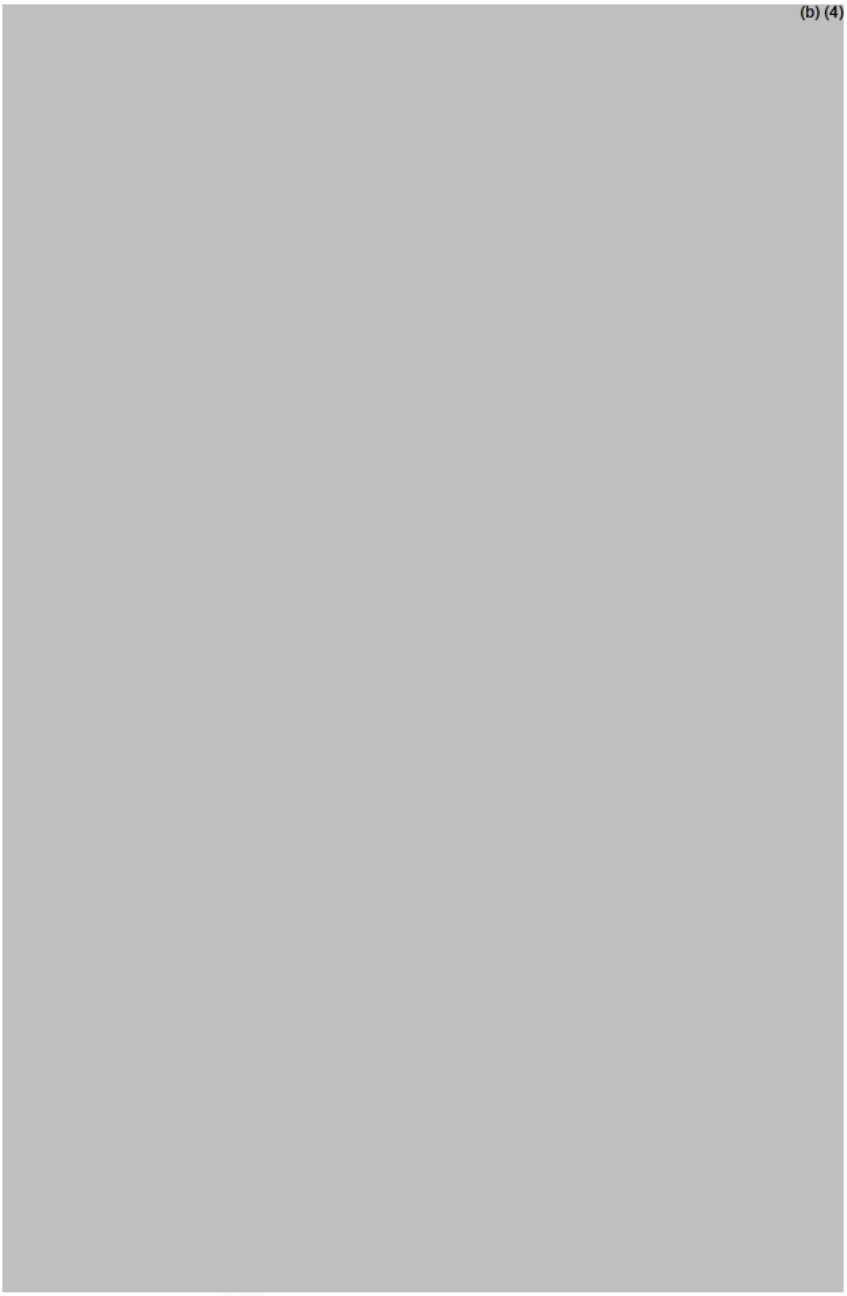


Figure 3. Exploded view of Naloxone Nasal Spray 4mg/0.25ml (16mg/ml)

4.1.1. Specific Changes to the Device Constituent – Post-CR Letter Issuance

Changes made in response to the CR Letter include the following:

- Naloxone dose is [redacted] (b) (4) 4mg.
- The filling volume is [redacted] (b) (4) 0.25ml.
- The N002 Nasal Injector [redacted] (b) (4) pre-assembled, ready to use.

4.2. Steps for Using the Device

1. Lay person flat on their back.
2. Peel the blister pack open from top left corner with the arrow. Remove the Naloxone Nasal Spray device.
3. Insert the nozzle all the way into one nostril.
4. Push the green plunger all the way down until it stops to give the dose. Remove the Naloxone Nasal Spray from nostril after dosing.
5. Get emergency help right away or call 911.
6. Wait 2 minutes. Watch person for response.
7. If no response, give a second dose with a new Naloxone Nasal Spray device in the opposite nostril following instructions in steps 2 to 4 above. Watch the person until emergency help arrives.
8. Throw away (dispose of) the used Naloxone Nasal Spray device in a place that is away from children.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device information provided for Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) is adequate to describe the combination product.	
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No	

5. FACILITIES & QUALITY SYSTEMS TRIAGE

5.1. Facilities Inspection Recommendation

Firm Name:	International Medication Systems, Ltd. (IMS)
Address:	1886 Santa Anita Avenue South El Monte, CA 91733
FEI:	2016148
Responsibilities:	Manufacturing, packaging, labeling and control operations, distribution, as well as release and stability testing of drug product
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☑ Inspection was conducted 5/17/2022 to 5/25/2022. The inspection covered drug CGMP and was classified VAI. A prior inspection was conducted 7/12/2021 to 7/16/2021 as a post-approval inspection that covered the firm's Quality, Materials, Facilities & Equipment, Manufacturing, and Packaging & Labeling systems as relating to the production of an injectable pre-filled syringe. The inspection was classified NAI. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
Inspection Recommendation:	

☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

5.2. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☑ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☑ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☑ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment
The proposed combination product is a Naloxone Nasal Spray intended to be administered to people who are suffering from a suspected and/or confirmed overdose of opioids. The final combination product is considered emergency use and has the possibility to be used for a vulnerable population. Additionally, if the product is not delivered correctly, the person suffering from an overdose may expire. Based on these, there is a high risk of cGMP issues.

5.3. Facilities & Quality Systems Review Triage Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW RECOMMENDATIONS

Facilities Inspection Recommendation:
☑ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance
☐ No Inspection ☐ N/A (Select this is a Facilities review is not being conducted)

Site(s) needing inspection:

International Medication Systems, Ltd. (IMS)
1886 Santa Anita Avenue

South El Monte, CA 91733
Quality System Review Required: ☑ Yes ☐ No ☐ N/A
Reviewer Comments See Section 12 for review of Facilities Inspection and/or Quality Systems Review

6. LABELING

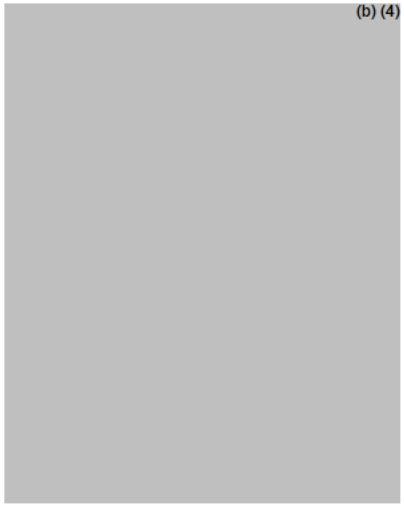


Figure 4. Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) container label

Figure 5. Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) peel lid label

Figure 6. Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) carton label

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
The labeling provided for the combination product includes the following:

- Prescribing Information: Indications & Usage, Dosage & Administration, Dosage Forms & Strengths, Contraindications, Warnings & Precautions, Adverse Reactions, Use in Specific Populations, Description, Clinical Pharmacology, Nonclinical Toxicology, How Supplied/Storage & Handling, Patient Counseling Information
- Patient Information: most important information to know, what it is, who should not use, information to tell HCP, how to use, possible side effects, how to store, general information, ingredients
- Instructions for Use
- Carton, blister, and device labels

The Sponsor also provided side-by-side labeled comparisons between the previously provided labels in the original submission versus the labels changed based on CR deficiencies. The changes made are specific to the revised dosage, fill volume, and instructions.

6.2. Device Specific Labeling Review

Reviewer Comments
The FDA guidance titled "Nasal Spray and Inhalation Solution, Suspension, and Spray Dug Products – Chemistry, Manufacturing, and Controls Documentation" (https://www.fda.gov/media/70857/download) includes a section on labeling recommendations for the label and package inserts. The applicable recommendations outlined by the guidance (e.g., amount of drug, fill weight, storage conditions, manufacturing details, prescription symbols, etc.) were provided in the labeling. Other elements such as number of sprays, shake instructions, priming sprays, and cleaning were not included as this is a single use device that does not require priming or shaking. The Instructions for Use will be further analyzed in the human factors review.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by
☐ Insert Consultant Name ; The full memo is located in Appendix B.
☑ The Lead Reviewer
Below is a summary of the review & recommendation:

See above.

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The provided labeling for Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) combination product includes all required elements from a device perspective.	
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No	

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A

Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
The adequacy of the outlined design control activities will be reviewed in their respective sections.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Pump Delivery (Spray Weight)	(b) (4)
Spray Pattern	
Plume Geometry	
Droplet Size Distribution	
Spray Content Uniformity	

	(b) (4)
Actuation Force (Break/Glide Force)	

Reviewer Comments

The Essential Performance Requirements (EPRs) outlined for the Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) combination product are aligned with EPRs typically assessed for nasal spray devices. The appropriateness and adequacy of the device to meet these specifications will be assessed in the performance testing. The specifications provided are aligned with the FDA guidance titled "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation" (https://www.fda.gov/media/70857/download) which state the following:

a. *In general, pump spray weight delivery acceptance criteria should control the weight of individual sprays to within "15 percent of the target weight and their mean weight to within "10 percent of the target weight. However, for small dosage pumps other acceptance criteria may be justified.*
b. *The acceptance criteria for spray pattern should include the shape (e.g., ellipsoid of relative uniform density) as well as the size of the pattern (e.g., no axis greater than x millimeters and the ratio of the longest to shortest axes should lie in a specified range).*
c. There is no acceptance criteria recommendations outlined in the guidance for plume geometry and droplet size distribution.
d. *The following acceptance criteria for spray content uniformity are recommended. However, alternative approaches (e.g., statistical) can be proposed and used if they are demonstrated to provide equal or greater assurance of SCU.*
    - *For acceptance of a batch (1) the amount of API per determination is not outside of 80 to 120 percent of label claim for more than 2 of 20 determinations (10 from beginning and 10 from end) from 10 containers, (2) none of the determinations is outside of 75 to 125 percent of the label claim, and (3) the mean for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim. If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside of 80 to 120 percent of the label claim, but none are outside of 75 to 125 percent of label claim and the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim, and additional 20 containers should be sampled for second-tier testing.*
    - *For the second tier of testing of a batch, the acceptance criteria are met if (1) the amount of API per determination is not outside of 80 to 120 percent of the label claim for more than 6 of all 60 determinations, (2) none of the 60 determinations is outside of 75 to 125 percent of label claim, and (3) the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.*

7.3. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The provided Essential Performance Requirements (EPRs) for Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) combination product aligns with FDA guidance and recommendations.	
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No	

8. RISK ANALYSIS

8.1. Hazard Analysis and Risk Summary Report

Evaluation of Risk Documents

Document	Comments
Risk Summary Report	The Risk Summary Report contains a section for hazard/risk identification in which 37 hazard risk factors were identified. The last identified hazard (AK) has 32 sub-risks associated with the overarching hazard identification. The table provided identifies the hazard code, type of FMEA, item/process steps, failure description, reason of failure, effect on procedure/patient, SR, PR, risk controls, and PR after RM. These hazards can be traced to the respective FMEAs reviewed below.

Table 1: Severity Levels and Ratings (SR)

Effect	Expected Consequence	Rating Rank (Score)
Negligible	Result in inconvenience or temporary injury	1
Minor	Result in temporary injury or impairment not requiring professional medical intervention	2
Serious	Result in injury or impairment requiring professional medical intervention	3
Critical	Result in permanent impairment or life threatening injury	4
Catastrophic	Result in patient death	5

Table 2: Probability Levels and Ratings (PR)

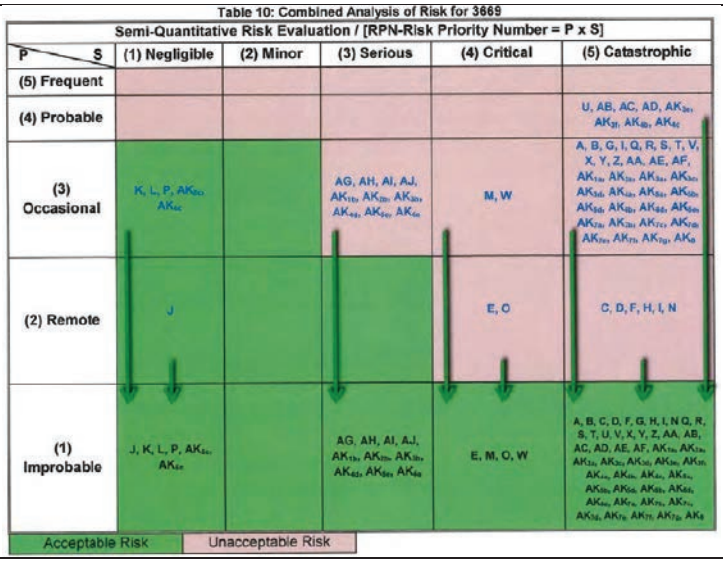
Probability Category	Probability of Occurrence		Probability as percentage range*	Rating Rank (Score)
	Lower Limit	Upper Limit		
Improbable		≤ 1 in 10,000	≤ 0.01%	1
Remote	> 1 in 10,000	≤ 1 in 1000	(0.01%, 0.1%]	2
Occasional	> 1 in 1000	≤ 1 in 100	(0.1%, 1%]	3
Probable	> 1 in 100	≤ 1 in 10	(1%, 10%]	4
Frequent	> 1 in 10	-	> 10%	5

* where "(" or ")" define a open range, i.e. not including "equal"; and "[" or "]" define a close range, i.e. including "equal".

Table 3: Risk Acceptability Evaluation

Semi-Quantitative Risk Evaluation / [RPN-Risk Priority Number = PR × SR]					
Severity / Probability	(1) Negligible	(2) Minor	(3) Serious	(4) Critical	(5) Catastrophic
(5) Frequent	Unacceptable [5]	Unacceptable [10]	Unacceptable [15]	Unacceptable [20]	Unacceptable [25]
(4) Probable	Unacceptable [4]	Unacceptable [8]	Unacceptable [12]	Unacceptable [16]	Unacceptable [20]
(3) Occasional	Acceptable [3]	Acceptable [6]	Unacceptable [9]	Unacceptable [12]	Unacceptable [15]
(2) Remote	Acceptable [2]	Acceptable [4]	Acceptable [6]	Unacceptable [8]	Unacceptable [10]
(1) Improbable	Acceptable [1]	Acceptable [2]	Acceptable [3]	Acceptable [4]	Acceptable [5]

Semi-Quantitative Risk Evaluation per ISO 14971

	
uFMEA	The purpose of this document is to describe the process by which the identification and elaboration of failure modes associated with the use of the combination product. The table includes the hazard code, item/process steps, failure description, reason of failure, effect on procedure/patient, SR, PR, initial RPN, risk controls, PR after RM, and adjusted RPN. The following failure descriptions were provided in the uFMEA table: a. Product is stored outside of labeled temperature range b. Product is not stored protected from light c. User is unable to open carton d. User is unable to open blister pack e. Patient is positioned other than flat on their back f. Device is primed prior to inserting spray into nostril g. Dose is administered in location other than nostril h. Spray tip is not fully inserted into nostril i. Device is over-inserted in nostril j. Plunger is pushed too quickly k. Plunger is pushed too slowly l. Plunger is not pushed completely m. Plunger is pulled out of barrel and re-inserted n. Device is left in nostril after drug delivery o. Patient is not monitored long enough and second dose is administered p. Patient is not monitored long enough and second dose is administered too soon after first dose q. Patient is not monitored adequately and second dose is administered longer than two (2) minutes after first dose r. Patient is not monitored adequately and the second dose is not administered s. Used nasal spray delivery device is reused t. Second dose is administered in the same nostril The uFMEA should be considered in review of the human factors validation study (deferred to DMEPA). The risk controls in place for the aforementioned failure descriptions include stability testing, labeling, human factors, design of the injector, and training.

dFMEA	The purpose of this document is to describe the process by which the identification and elaboration of failure modes associated with the design of the combination product was conducted to determine risks and subsequent effects. The table includes the hazard code, item/process steps, failure description, reason of failure, effect on procedure/patient, SR, PR, initial RPN, risk controls, PR after RM, and adjusted RPN. The following failure descriptions were provided in the dFMEA table: a. Assembled intranasal tip becomes detached from the injector b. The medication vial is able to be removed from the injector c. Nasal spray unit leaks d. Intranasal tip does not allow delivery of medication into the nostrils of intended user e. Plunger does not disappear into the injector upon administration of medication f. Damaged and/or defective components used in the manufacturing process g. Device/injector component fail or break due to incorrect cannula dimensions or incorrect component dimensions h. Combination product Actuation Force exceeds specification due to inadequate (b) (4) i. Combination product Actuation Force does not meet specification due to inadequate cannula dimensions/performance j. Combination product does not meet Pump Delivery or Spray Content Uniformity specifications due to improper stopper height, cannula length, vial length, diameter of components, centering guide, cannula specifications k. Combination product does not meet Spray Pattern, Plume Geometry, or Droplet Size Distribution specifications due to improper nasal tip height or IN tip hole size l. Combination product is not stable in storage m. Damaged combination product n. Packaging does not provide protection from light o. Device/injector contaminate medication p. Medication is contaminated q. Device components are incompatible with medication r. Rubber stopper and/or nasal spray device are not biocompatible The failure descriptions categorized with an RPN of 5 (Severity 5, Occurrence 1) are mitigated through the (b) (4), assembly process validation, finished product release testing, leak testing, validated molding process, stability testing, verification testing of EPRs, human factors validation study, quality assurance testing and visual inspection (pull testing), validated (b) (4) process, and shipping study.
pFMEA	The purpose of this document was to describe the process by which the identification and elaboration of failure modes associated with the manufacturing process of the combination product was conducted to determine risks and subsequent effects. The table includes the hazard code, item/process steps, failure description, reason of failure, effect on procedure/patient, SR, PR, initial RPN, risk controls, PR after RM, and adjusted RPN. The following failure descriptions were provided in the pFMEA: a. Components received with dimensions out of specification b. Components received with nonfunctional requirements out of specification c. Raw materials are out of specification

	d. Molded component dimensions are out of specification e. Molded components are incompatible with medication f. Product can't be dispensed directly into nostrils (incorrect molding) g. Essential Performance Requirements (EPRs) out of specification due to incorrectly molded components or incorrect assembly of nasal tip h. Assembled injector is non-functional due to incorrect manufacturing and/or components i. High bioburden count/particulate matter j. Non-homogenous solution k. Potency/pH out of specification l. Adulterated medication m. Contaminated medication n. Filling volume error (low/high) o. High Actuation Force during administration due to inadequate (b) (4) p. Missing and/or wrong packaging components q. Incorrect/illegible label r. Incorrect pre-assembly s. Damage during shipping A majority of the failure descriptions above have been categorized with an RPN of 5 (Severity 5, Occurrence 1). These are mitigated through inspection of incoming raw materials/components, vendor qualifications and audits, finished product release testing, molding process validation, quality assurance inspections, stability testing, human factors validation study, assembly process validation and visual inspections during assembly, controlled drug substance procedures, (b) (4), environmental monitoring, and inspection of labels.

Reviewer Comments
In review of the FMEAs provided for the final finished combination product, the following will be communicated to the Sponsor in the CR letter for this submission:

(b) (4)

Fault Tree Analysis
The FTA shown below was obtained from the Risk Summary Report. Additional information on the FTA is provided in the reliability report provided in the submission. The FTA was conducted to identify root causes and events that may contribute to product failure.

Reviewer Comments
According to the draft FDA guidance titled "Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA: Guidance for Industry and Food and Drug Administration Staff" (https://www.fda.gov/media/137158/download), the fault tree should focus on failure to achieve the reliability specifications. The following should be considered for the FTA:

a. Design and manufacturing elements should be considered for the fault tree analysis for the purposes of establishing the reliability of the emergency-use injector to perform as intended, without failure, for a given time interval under specified conditions;
b. The probability data for each basic event should be included in the fault tree;
c. The analysis should consider potential common cause failures and whether assumptions of independence of events are supportable;
d. Any risk analyses used to support the fault tree analysis should be included in the reliability report;
e. Data should be provided to support the reliability specification for the top-level failure mode is verified and validated; and,
f. The basic events in the fault tree analysis should be linked to appropriate design and/or manufacturing controls.

(b) (4)

Through numerous interactions with the Sponsor, they have made the necessary revisions to the Fault Tree Analysis to ensure that all potential failure modes and failure rates are adequately assessed. Please see below for the Information Requests and responses associated with the revisions to the Fault Tree Analysis. Of note, the Sponsor has concurrently made revisions to the dFMEA and pFMEA based on the requested changes.

(b) (4)

8.2. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor has made the necessary revisions to the Fault Tree Analysis required for an adequate assessment of potential failure modes and associated failure rates.	
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No	

	Date Sent:	Date/Sequence Received:

	12/21/2022	12/30/2022
Mid-Cycle Deficiency #1	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	The above is the FTA provided in response to the mid-cycle deficiencies. This FTA includes probability calculations and the top-level failure mode of "Failure to deliver full intended dose". This is adequate. However, it does not appear that the FTA considers all failure modes associated with each component(s) and their interactions. Further it is unclear to what capacity the EPRs for the device constituent were included. Further, there is a high amount of remaining S5 level risks with a probability of 1. This demonstrates that there is a risk of 'Catastrophic' risks occurring to patients for an emergency-use product.
Response Adequate:	☐ **Yes** ☑ **No, See Information Request #1 & #2**

Follow-On Deficiency	**Date Sent:** **1/5/2023**	**Date/Sequence Received:** **1/18/2023**
Information Request #1 & #2	(b) (4)	

	(b) (4)
Sponsor Response	

	(b) (4)
Reviewer Comments	**Information Request #1** The Sponsor provided a revised dFMEA in Sequence 0062 Module 3.2.R. This revised dFMEA contains more risks with associated failure modes, effects, and risk controls. The dFMEA contains failure modes and risk controls for risks associated with each EPR if unable to meet established specifications. The dFMEA is acceptable. **Information Request #2** The Sponsor provided a revised Fault Tree Analysis in Sequence 0062 Module 3.2.R. The revised FTA contains more detail and specific EPR failure modes with traceability to "Failure to deliver full dose" with a reliability of (b) (4)%. The FTA provided does not include all of the necessary details needed to assess the adequacy of the analysis.
Response Adequate:	☐ **Yes** ☑ **No, See IR #6 Sent on 1/31/2023**

Follow-On Deficiency	**Date Sent:** **1/31/2023**	**Date/Sequence Received:** **1/18/2023**
Information Request #6	(b) (4)	

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	(b) (4)
Reviewer Comments	The provided information is not sufficient to address concerns related to component interactions and failure mode assignment.
Response Adequate:	☐ **Yes** ☑ **No, See IR #7 Sent on 2/9/2023**

Follow-On Deficiency	**Date Sent:** **2/9/2023**	**Date/Sequence Received:** **2/14/2023**
Information Request #7	(b) (4)	

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Reviewer Comments	In response to the above Information Request, the Sponsor provided a tolerance stack analysis and revised Fault Tree Analysis. The tolerance stack analysis included an assessment of critical dimensions and their potential interference which would impact performance of the final finished combination product. The critical dimensions, acceptance criteria, and associated figures are included below. Each dimension associated with the critical dimension, risk, and objective are shown with their respective tolerances. (b) (4)

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	(b) (4)
	The revised Fault Tree Analysis includes potential failure modes associated with the vial holder and nasal tip insert as requested. The analysis includes interactions with multiple components with respect to dimensions and positioning. The analysis includes a table for each identified failure mode that includes the calculations conducted to obtain the failure rate. The failure rates have been calculated using: • Inspection criteria (# of rejects / units inspected) – these vary depending on the amount of units inspected for each component/assembly • IMS AQL • Vendor AQL

	• Measurement data from molding process inspections during manufacturing of component lots (b) (4) Additionally, the Sponsor has revised the Fault Tree Analysis to ensure no failure rates are double-counted which could inflate the probability of a successful injection. (b) (4)
Response Adequate:	☐ **Yes** ☑ **No, See IR # Sent on 2/21/2023**

Follow-On Deficiency	**Date Sent: 2/21/2023**	**Date/Sequence Received: 2/22/2023**
Information Request #8	(b) (4)	
Sponsor Response		
Reviewer Comments	Below is an excerpt of the table provided.	

	(b) (4)
Response Adequate:	☐ **Yes** ☑ **No, see IR #9 Sent on 2/23/2023**

Follow-On Deficiency	**Date Sent: 2/23/2023**	**Date/Sequence Received: 2/22/2023**
Information Request #9	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	The explanation for the AQL calculations is clear after justification from the Sponsor. However, the Sponsor has not provided a rationale for RE 2 and RE 3 and how these do not impact reliability of the final finished device.
Response Adequate:	☐ **Yes** ☑ **No, See IR #10 & #11 Sent on 2/23/2023**

Follow-On Deficiency	**Date Sent:** 2/23/2023	**Date/Sequence Received:** 3/6/2023
Information Request #10 & #11	(b) (4)	
Sponsor Response		

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	(b) (4) [redacted]
Reviewer Comments	The Sponsor has revised a majority of the accept/reject values to be AC 0 / RE 1 to ensure the reliability of the device is maintained. The following failure mode accept/reject values differ from AC 0 / RE 1: (b) (4) [redacted] The SOP for Injector Assembly includes an inspection of the line/machine/sub-assembly tools, in-process sampling, finished component testing, and documentation. The SOP for finished product physical tests include random selection procedure, sampling schedule, and sampling plan. The revised Fault Tree Analysis is acceptable.
Response Adequate:	☑ **Yes** ☐ **No**

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

The following information was obtained from Sequence 0049. Additional information requested in the mid-cycle information requests was obtained from Sequence 0057.

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Pump Delivery (Spray Weight)	(b) (4)	N=50 95% Confidence 99.999% Reliability Two-Sided	Y	Y	Y
Spray Pattern		N=80 95% Confidence 99.999% Reliability One-Sided	Y	Y	Y
Plume Geometry		N=50 95% Confidence 99.999% Reliability Two-Sided	Y	Y	Y
Droplet Size Distribution		N=50 95% Confidence 99.999% Reliability Two-Sided	Y	Y	Y
Spray Content Uniformity		N=400 95% Confidence 99.999% Reliability Two-Sided	Y	Y	Y

	(b) (4)				
Actuation Force (Break/Glide Force)		N=50 95% Confidence 99.999% Reliability One-Sided	Y	Y	Y

Reviewer Comment

The data provided was obtained from Essential Performance Requirement (EPR) testing on devices having undergone transportation testing and accelerated aging to the end of the anticipated shelf-life. The samples tested were obtained from three (3) lots 111920A, 112520A, and 120220A. The shipping study was performed according to ISTA 3A. Once the shipping study was completed, all units were placed in accelerated aging at 42C for NLT 6 months. After accelerated aging, the units were placed at 20 to 25C for 17 weeks prior to testing. In accelerated aging conditions, the Sponsor states the devices were aged 28 weeks and 4 days (200 days total). With the additional 17 weeks of storage at ambient temperatures, the devices were aged for a total of 319 days.

It is unclear if other factors were considered in the foreseeable worst-case testing provided such as environmental temperature, humidity, storage orientation/conditions, vibration, shock, actuation orientation, etc.. In response to the mid-cycle information requests, the Sponsor provided a rationale for each condition tested and how it demonstrates worst-case conditions for the reliability of the device. An overview of their rationale is provided below:

(b) (4)

(b) (4)

9.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)
Pump Delivery (Spray Weight)	(b) (4)		Minimum: 102.7% Maximum: 108.4% Mean: 105.6% Standard Deviation: 1.58% K min: 5.359 K actual: 5.930	Y	Y	Y
Spray Pattern			Dmax Minimum: 20.16 Maximum: 24.29 Mean: 21.87	Y	Y	Y

	(b) (4)	Standard Deviation: 0.842 <u>Ovality</u> Minimum: 1.103 Maximum: 1.239 Mean: 1.153 Standard Deviation: 0.028 K min: 4.944 K actual: 21.548			
Plume Geometry		<u>Angle</u> Minimum: 34.2 Maximum: 37.4 Mean: 35.8 Standard Deviation: 1.031 <u>Width</u> Minimum: 18.48 Maximum: 20.28 Mean: 19.39 Standard Deviation: 0.593 K min: 5.359 K actual: 8.918	Y	Y	Y
Droplet Size Distribution		<u>D10</u> Minimum: 21.66 Maximum: 25.47 Mean: 23.46 Standard Deviation: 0.645 <u>D50</u> Minimum: 45.17 Maximum: 50.51 Mean: 48.29 Standard Deviation: 0.980	Y	Y	Y

			D90 Minimum: 97.19 Maximum: 102.0 Mean: 99.76 Standard Deviation: 1.129 Span Minimum: 1.485 Maximum: 1.714 Mean: 1.581 Standard Deviation: 0.042 K min: 5.359 K actual: 13.614			
Spray Content Uniformity	[redacted] (b) (4)		Minimum: 101.6 Maximum: 112.2 Mean: 103.9 Standard Deviation: 1.180 K min: 4.698 K actual: 9.969	Y	Y	Y

	(b) (4)				
Actuation Force (Break/Glide Force)		<u>Glide Force</u> Minimum: 8.19 Maximum: 20.63 Mean: 14.25 Standard Deviation: 3.324 <u>Break Loose Force</u> Minimum: 4.09 Maximum: 6.79 Mean: 5.60 Standard Deviation: 0.629 K min: 5.164 K actual: 7.748	N	Y	Y

Reviewer Comment
A summary table of the results is shown below.

#	Method	Item Tested	Specification	N	Passed	Failed	Mean	S.D.	Range
1	Pump Delivery	Individual, %	(b) (4)	50	50	0	106%	1.6%	(103% , 108%)
2	Spray Pattern	Ovality		80	80	0	1.2	0.028	(1.1 , 1.2)
		Size, Dmax			80	0	22	0.84	(20 , 24)
3	Plume Geometry	Angle		50	50	0	36	1.0	(34 , 37)
	Shape	Width			50	0	19	0.59	(18 , 20)
4	Spray Content Uniformity (SCU)	API, %LC		400	400	0	104%	1.2%	(102% , 112%)
5	Droplet Size Distribution	D_{v10}		50	50	0	23	0.65	(22 , 25)
		D_{v50}			50	0	48	0.98	(45 , 51)
		D_{v90}			50	0	100	1.1	(97 , 102)
		Span			50	0	1.6	0.042	(1.5 , 1.7)
6	Actuation Force	Break Force		50	50	0	6	0.63	(4 , 7)
		Glide Force			50	0	14	3.3	(8 , 21)
				680	1010	0			

The verification methods were not provided for the EPRs tested. In response to the mid-cycle information requests, the Sponsor provided a document in Sequence 0057 titled "LTM-19-285" that contains the laboratory test methods. However, the method for actuation force was not provided.

Additionally, it is unclear how the actual k values were calculated as hand calculations do not result in the same numbers. However, the calculations performed indicate the k values are above the minimum threshold.

In regards to the target k values for each EPR, the literature available to determine these parameters is limited. Annex B of ISO 11608-1 only provides target k values up to a reliability of 99.99%. NASA's technical memorandum includes target k values up to a reliability of 99.999%; however, the sample size included is limited to N=2. As such, the Sponsor has expanded the tolerance tables for one-sided and two-sided k values to obtain target parameters for each EPR tested. The Sponsor's results were compared to the ISO standard and NASA documentation to ensure the calculations were correct. All results were aligned excluding N=6 p=0.999 in regards to the ISO standard; however, the result was aligned with NASA documentation.

a. One-Sided Tolerance Limit Factors, Gamma = 0.950

Amphastar, Data Results utilizing VBA coding

N	P = 0.750	P = 0.900	P = 0.950	P = 0.975	P = 0.990	P = 0.999	P = 0.999 9	P = 0.999 99
2	11.763	20.581	26.260	31.257	37.094	49.276	59.304	68.010
10	1.465	2.355	2.911	3.402	3.981	5.203	6.219	7.105
20	1.166	1.926	2.396	2.810	3.295	4.318	5.167	5.906
50	0.960	1.646	2.065	2.432	2.862	3.766	4.513	5.164
100	0.870	1.527	1.927	2.276	2.684	3.539	4.247	4.862
200	0.809	1.450	1.837	2.175	2.570	3.395	4.077	4.670

ISO-11608-1:2014, Table B.1

N	P = 0.750	P = 0.900	P = 0.950	P = 0.975	P = 0.990	P = 0.999	P = 0.999 9	P = 0.999 99
2	11.763	20.581	26.260	31.257	37.094	49.276	59.304	-
10	1.465	2.355	2.911	3.402	3.981	5.203	6.219	-
20	1.166	1.926	2.396	2.810	3.295	4.318	5.167	-
50	0.960	1.646	2.065	2.432	2.862	3.766	4.513	-
100	0.870	1.527	1.927	2.276	2.684	3.539	4.247	-
200	0.809	1.450	1.837	2.175	2.570	3.395	4.077	-

b. Two-Sided Tolerance Limit Factors, Gamma = 0.950

Amphastar, Data Results utilizing VBA coding

N	P = 0.750	P = 0.900	P = 0.950	P = 0.975	P = 0.990	P = 0.995	P = 0.999	P = 0.999 9	P = 0.999 99
2	22.383	31.092	36.519	41.308	46.944	50.813	58.844	68.728	77.348
10	2.008	2.856	3.393	3.871	4.437	4.827	5.640	6.646	7.525
20	1.624	2.319	2.760	3.154	3.621	3.943	4.616	5.450	6.180
50	1.398	1.999	2.382	2.723	3.129	3.409	3.995	4.722	5.359
100	1.311	1.875	2.234	2.555	2.936	3.199	3.750	4.433	5.032
200	1.258	1.798	2.143	2.451	2.816	3.069	3.598	4.253	4.829

ISO-11608-1:2014, Table B.2

N	P = 0.750	P = 0.900	P = 0.950	P = 0.975	P = 0.990	P = 0.995	P = 0.999	P = 0.999 9	P = 0.999 99
2	22.383	31.092	36.519	41.308	46.944	50.813	58.844	-	-
10	2.008	2.856	3.393	3.871	4.437	4.827	5.640	-	-
20	1.624	2.319	2.760	3.154	3.621	3.943	4.616	-	-
50	1.398	1.999	2.382	2.723	3.129	3.409	3.995	-	-
100	1.311	1.875	2.234	2.555	2.936	3.199	3.750	-	-
200	1.258	1.798	2.143	2.451	2.816	3.069	3.598	-	-

9.1.3. Transportation Testing

The proposed combination product has undergone simulated shipping according to ISTA 3A. The acceptance criteria and pass/fail results for the shipping study are included below.

Table 3. Acceptance Criteria (PVP-33-21, Section 7.0)			
	Acceptance Criteria	Pass / Fail	Report Section
	ISTA 3A Ship Test		
7.1	(b) (4)	Pass	4.0
7.2		Pass	4.3
	EPR Evaluations		
7.3	(b) (4)	Pass	4.5
7.4		Pass	4.6
7.5		Pass	4.6

Reviewer Comment
The objective of the study states "To demonstrate the protective performance of IMS packaging for IMS final product Naloxone HCl Nasal Spray, 16mg/ml (0.25ml). Lot Prefix NA (b) (4), each packages as a pre-filled 3ml (b) (4) glass vial with a 3ml Nasal Injector (b) (4) and a 3ml Vial Holder (b) (4) and sealed into a blister pack" (b) (4) The Sponsor should clarify what version of the device was used for this study (b) (4)

The Sponsor has clarified in their response to the mid-cycle information requests that the TBM final finished combination product was utilized for testing.

9.1.4. Stability

The Sponsor is requesting a 24-month expiration dating for the Naloxone HCl Nasal Spray 4mg/0.25ml (16mg/ml) combination product. The Sponsor has performed the following stability studies and provided the data that is available:

- Long-term: 18 months at 25°C (inverted and upright)
- Intermediate: 18 months at 30°C (inverted and upright
- Refrigerated: 18 months at 2 – 8°C (inverted and upright)
- Accelerated: 18 months at 40°C

- Photostability: Samples were stored following the ICH Guidance for Industry Q1B "Stability Testing: Photostability Testing of New Drug Substances and Products". Testing may be carried out within twelve months from the initiation of the stability program using samples from the 25°C ± 2°C storage condition.
- Thermal Cycling: Samples were frozen for two (2) days between -10°C and -20°C then transferred to 40°C ± 2°C for two (2) days as one cycle. This was repeated for three (3) cycles. Testing may be carried out within twelve months from the initiation of the stability program using samples from the 25°C ± 2°C storage condition.

Reviewer Comment

The sample sizes for each stability test condition was not provided. It is unclear if the results provided were for one (1) sample or the average data obtained from a larger sample size. Further, the Sponsor should clarify whether the accelerated aged samples were kept in the chamber for 18 months or whether the data represents 18 months of shelf-life and provide the applicable parameters for review.

In response to the mid-cycle information requests sent to the Sponsor, they have identified the accelerated aging having been performed for information only and is not representative of the intended shelf-life. At this time, the Sponsor has 18 months of shelf-life data which may be supported. However, there is not an adequate amount of data to support a 24-month shelf-life.

Additionally, the Sponsor has clarified the sample sizes – please see the table below.

Table 6a-1. Sample Sizes for Each EPR Test at Each Required Test Interval

Temperature Storage Conditions	2°C-8°C, 25°C±2°C, 30°C±2°C, and 40°C±2°C				
EPR Tests	Test Intervals				
	Initial	6 Mo.	9 Mo.[1]	12 Mo.	24 Mo.
Pump Delivery (Spray Weight)	5	5	5	5	5
Spray Pattern	5	5	5	5	5
Plume Geometry Shape	5	5	5	5	5
Spray Content Uniformity (SCU)[2]	10+20	10+20	10+20	10+20	10+20
Droplet Size Distribution	5	5	5	5	5
Actuation Force (Break/Glide Force)	200	15	15	15	15

[1] The 9-month test interval is required only for 40°C±2°C storage condition.

[2] If the first 10 dosage units does not meet the 1st Tier specification, additional 20 units are required for 2nd Tier testing

The Sponsor provided summary results for stability samples for refrigerated, long-term, intermediate, and accelerated conditions. The summary table is provided below.

Table 6a-2. Data Analysis of each Essential Performance Requirement (EPR)

EPR Tests	Stability Storage Condition: Refrigerated (2°C -8°C)	Long-term (25°C±2°C)	Intermediate (30°C±2°C)	Accelerated (40°C±2°C)
Pump Delivery (Spray Weight) (spec (b) (4)				
minimum:	95.0%	95.4%	93.1%	94.5%
maximum:	112.1%	113.1%	112.8%	113.4%
standard deviation:	4.6%	4.6%	5.2%	4.8%
average:	104.2%	104.0%	103.3%	102.7%
k value:	2.35	2.36	2.26	2.55
Spray Pattern				
-Ovality: (spec: (b) (4)				
minimum:	1.1	1.1	1.1	1.1
maximum:	1.3	1.3	1.3	1.3
standard deviation:	0.04	0.05	1.2	0.05
average:	1.2	1.2	0.03	1.2
k value:	15.50	10.97	17.81	13.01
-Pattern Size: (spec (b) (4)				
minimum:	19.9	20.0	19.9	20.7
maximum:	26.2	26.2	26.2	28.4
standard deviation:	1.5	1.6	1.6	1.9
average:	22.9	22.9	22.8	23.7
k value:	11.09	10.67	10.67	8.62
Droplet Size Distribution				
-D10: (b) (4)				
minimum:	21.0	20.5	15.0	21.0
maximum:	25.6	25.1	25.5	25.5
standard deviation:	1.0	0.91	1.3	0.84
average:	22.9	23.0	23.0	23.0
k value:	7.26	7.68	5.51	8.35
-D50: (spec: (b) (4)				
minimum:	44.4	42.5	44.4	44.4
maximum:	52.5	56.3	50.6	56.5
standard deviation:	1.6	1.7	1.2	1.6
average:	48.0	48.0	47.9	47.9
k value:	7.04	6.41	9.02	6.9
Actuation Force (Break/Glide Force)				
-Break Force: (spec: (b) (4)				
minimum:	3.0	3.0	3.0	3.0
maximum:	44.4	42.3	42.3	42.3
standard deviation:	6.9	6.8	6.5	6.5
average:	18.2	18.3	17.9	16.8
k value:	4.47	4.55	4.78	4.93

EPR Tests	Stability Storage Condition: Refrigerated (2°C -8°C)	Long-term (25°C±2°C)	Intermediate (30°C±2°C)	Accelerated (40°C±2°C)
Spray Conent Uniformity (SCU) (spec (b) (4)				
minimum:	97.0%	96.9%	96.9%	97.0%
maximum:	108.6%	108.6%	108.6%	108.6%
standard deviation:	2.7%	2.6%	2.1%	2.4%
average:	102.8%	103.1%	102.9%	103.1%
k value:	6.40	6.53	8.18	7.13
Plume Geometry Shape				
-Plume Angle: (spec (b) (4)				
minimum:	30.4	30.4	30.4	30.4
maximum:	41.4	41.4	41.4	41.4
standard deviation:	2.2	2.0	1.8	1.6
average:	35.4	35.2	34.9	34.8
k value:	4.40	4.92	5.46	6.02
-Plume Width: (spec (b) (4)				
minimum:	16.3	16.3	16.3	16.3
maximum:	22.7	22.7	22.7	22.7
standard deviation:	1.3	1.2	1.1	0.94
average:	19.2	19.0	18.9	18.9
k value:	4.64	5.15	5.83	6.53
Droplet Size Distribution (continued)				
-D90: (spec (b) (4)				
minimum:	93.0	96.3	92.4	90.4
maximum:	113.4	120.0	106.6	120.6
standard deviation:	3.3	3.8	2.6	3.3
average:	101.1	102.1	101.0	100.3
k value:	5.71	5.23	7.29	5.52
-Span: (spec (b) (4)				
minimum:	1.4	1.5	1.5	1.4
maximum:	1.9	2.0	1.9	1.9
standard deviation:	0.08	0.09	0.07	0.07
average:	1.6	1.6	1.6	1.6
k value:	4.66	4.14	5.45	5.56
Actuation Force (Break/Glide Force) (continued)				
-Glide Force: (spec: (b) (4)				
minimum:	1.2	1.1	1.2	1.2
maximum:	31.1	31.1	31.1	31.1
standard deviation:	8.5	8.5	8.5	8.2
average:	9.7	9.8	9.7	9.3
k value:	4.63	4.61	4.65	4.85

NOTE: Data analysis was tabulated up to latest EPRs test intervals (12 Mo.)

The data provided was obtained from 12-month stability samples that underwent EPR testing for each condition tested. There are instances for each condition in which the k values for the EPR(s) are not met for a 99.999% reliability. While the Sponsor has conducted transportation and aging for reliability samples, it is unclear why these samples would not meet the k value threshold for multiple EPRs and conditions.

9.1.5. Biocompatibility

The Sponsor has provided the following biocompatibility tests for the Naloxone Nasal Spray 4mg/0.25ml (16mg/ml). The product is classified as a mucosal/skin-contacting device with a contact duration of less than 24 hours. As such, the biocompatibility reports that will be reviewed include Cytotoxicity, Sensitization, and Irritation in accordance with the FDA guidance titled "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"" (https://www.fda.gov/media/85865/download).

Qualification – Biological Reactivity Testing	Results for Injector Lot No. Nasal Spray Injector: A110220E; Vial Holder: M101920E
• Acute Systemic Toxicity in CD-1 Mice (ISO 10993-11:2017)	Pass (no biologically significant differences between the test and control animals)
• ASTM Hemolysis – Direct and Extraction Methods (ISO 10993-4 and ASTM F 756-13)	Pass (Non-hemolytic)
• Cytotoxicity – MEM Elution Test (ANSI/AAMI/ISO 10993-5:2009)	Pass (not considered to have a cytotoxic effect)
• Maximization Test for Delayed-Type Hypersensitivity in Hartley Guinea Pigs (ISO 10993-10:2010)	Pass (Did not elicit sensitization reaction in animal)
• Intracutaneous (Intradermal) Reactivity Test in New Zealand White Rabbits (ISO 10993-10:2010)	Pass (no irritation per erythema and edema scores)
• Pyrogen Test in New Zealand White Rabbits (ISO 10993-11:2017 / USP<151>, Rev. 5/2016)	Pass (absent of pyrogen)

Biocompatibility Information Red = Inadequate or Unanswered Yellow = Focal Point

There is/are 1 tissue contacting products/components/materials.

Material compositions described?: Yes

Device has Special Considerations?: No

Table of Materials and Rationales

Component	Material	Type of Contact	Identical Material & Rationale
N002 Nasal Injector	(b) (4)	Direct	No, No Rationale

Rationale

Rationale: No rationale provided.

Biocompatibility Material 1:

Test Component/Material: N002 Nasal Injector / (b) (4)

Potential for Repeat Exposure?: Yes

Type of Tissue Contact: Surface Device: Mucosal Membrane

Duration of Contact: < 24 hours

Cytotoxicity Testing Red = Inadequate or Unanswered Yellow = Focal Point

Cytotoxicity testing conducted: Extraction Method (MEM Elution)

Test Article: 3ml Nasal Spray Injector with 3ml Vial Holder

Extraction Conditions	Methods	Results	Conclusion and Recommendation
(b) (4)	**Test System:** L-929 Mouse fibroblasts (monolayer) **Assessment Times:** Required: 37°C for 48 hr minimum **Proper Scale Used:** Yes **Deviations?:** No	**Cell Abnormalities:** No **Scores in controls as expected:** Yes	**Cytotoxic Potential:** Non-cytotoxic (Grade 0) **Recommendation:** Acceptable

Storage Conditions: Used by 24 hrs post-extraction			
Comments:			
Sensitization Testing **Red = Inadequate or Unanswered** **Yellow = Focal Point**			
Sensitization testing conducted: Yes, Guinea Pig Maximization Test (GPMT) **Test Article:** 3ml Nasal Spray Injector with 3ml Vial Holder			
Extraction Conditions	**Methods**	**Results**	**Conclusion and Recommendation**
(b) (4)	**Test System:** ≥ 10 Test & ≥ 5 Control Males &/or Females (nulliparous, not pregnant) **Proper Injections Given?:** Yes **Proper Procedure on Day 6?:** Yes **Proper Procedure on Day 7?:** Yes **Proper Procedure after 14 Days?:** Yes **Assessment Times after Challenge:** 24 and 48 hours **Deviations?:** No	**Normal & No Deaths?:** Normal appearance, no deaths **Polar extract score < 1.0?:** No, and scores of ≥ 1.0 are seen in control animals **Non-Polar extract score < 1.0?:** No, and scores of ≥ 1.0 are seen in control animals **Positive Control ≥ 1.0?:** Yes	**Sensitizing Potential:** Non-Sensitizer **Recommendation:** Acceptable
Comments: The polar and non-polar test groups had multiple animals that had a sensitization grade of 1. However, the negative control groups for polar and non-polar groups also had sensitization grades of 1. The positive control group had a mean sensitization grade of 3. The results are acceptable though uncommon.			
Irritation Testing **Red = Inadequate or Unanswered** **Yellow = Focal Point**			
Irritation testing conducted: Yes, Intracutaneous Irritation Test **Test Article:** 3ml Nasal Spray Injector with 3ml Vial Holder			
Extraction Conditions	**Methods**	**Results**	**Conclusion and Recommendation**
(b) (4)	**Test System:** ≥ 3 Rabbits **Proper Injections Given?:** Yes **Assessment Times:** 24hr, 48hr, and 72hr **Proper Scoring?:** Yes	**Normal & No Deaths?:** Normal appearance, no deaths **Polar extract score:** ≤ 1.0 **Non-Polar extract score:** ≤ 1.0	**Irritant Potential:** Non-Irritant **Recommendation:** Acceptable

Reviewer Comments
The Sponsor provided the classification and duration for the Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) in response to the mid-cycle information request. This is an acceptable classification.

The red component of the biocompatibility table above was discussed with a biocompatibility consultant within OHT3C. After review of the test report and an overview of the product, the test and control are similar indicating that the higher than normal grade levels may be negligible.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The verification of Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) has been resolved through interactive requests for information.	
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No	

	Date Sent: 12/21/2022	**Date/Sequence Received:** 12/30/2022
Mid-Cycle Deficiencies #2-7	(b) (4)	

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	(b) (4) [redacted]
Reviewer Comments	**Mid-Cycle Deficiency #2** The worst-case conditions provided appear to be aligned with the typical worst-case testing provided for similar emergency use devices. **Mid-Cycle Deficiency #3** The devices were aged 28 weeks and 4 days (total of 200 days) to meet the 24-month shelf-life for the final finished combination product. The devices were then stored for an additional 17 weeks prior to EPR testing. **Mid-Cycle Deficiency #4** The documentation provided does not include the verification method for actuation force. **Mid-Cycle Deficiency #5** The response is acceptable. **Mid-Cycle Deficiency #6** The Sponsor has clarified the accelerated aging study (separate from reliability testing/aging). However, in the conditions outlined, there are EPRs that do not meet the 99.999% reliability intended for the emergency use product. **Mid-Cycle Deficiency #7** The response is adequate. Given that the device is an emergency use product that will not be used regularly and similar devices have been classified as a surface device with limited mucosal membrane contact duration, the categorization is acceptable.
Response Adequate:	☐ **Yes** ☑ **No, See Information Request #3 & #4**

Follow-On Deficiency	**Date Sent:** **1/5/2023**	**Date/Sequence Received:** **1/18/2023**
Information Request #3 & #4	**Information Request #3**	

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	(b) (4)
Reviewer Comments	**Information Request #3** The response is acceptable. **Information Request #4** The response is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9.3. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review
☑ There are clinical studies for review
This information was obtained from the following **documents**:
Module 5.3.3 Reports of Human Pharmacokinetic Studies

- Study A3: A Randomized, Evaluator-Blinded, Single-Dose, Four-Treatment, Four-Period, Crossover, Fasting, Pharmacokinetic and Tolerability Study of Intranasal Naloxone HCl (N002) in Healthy Adult Volunteers
- Study A4: A Randomized, Double-Blinded, Single-Dose, Two-Treatment, Two-Period, Crossover Study of Intranasal Naloxone HCl (N002) Effect on Olfactory

<table>
<tr><th>Study Name</th><th>A Randomized, Evaluator-Blinded, Single-Dose, Four-Treatment, Four-Period, Crossover, Fasting, Pharmacokinetic and Tolerability Study of Intranasal Naloxone HCl (N002) in Healthy Adult Volunteers</th></tr>
<tr><td>Study Type</td><td>This was a randomized, evaluator-blinded, four-treatment, crossover PK study conducted in healthy volunteers.</td></tr>
<tr><td>Objectives/Endpoints</td><td>This study aimed to evaluate PK and Safety/Tolerability profiles of the proposed intranasal (IN) product, N002. The PK parameters which characterize the N002 efficacy and safety evaluation were compared between IN deliveries of N002, and intramuscular (IM), or intravenous (IV) injections of Naloxone in healthy volunteers.

Primary PK Endpoints: AUC_{0-t^*}, t’
Secondary PK Endpoints: C_{max}, t_{max}, AUC_{0-inf}, AUC_{0-6hrs}, $C^{IN}(t^*)$
Additional Endpoints: Relative bioavailability of IN Naloxone treatments versus IM and IV Naloxone
Tolerability Evaluations: Nasal and Oropharyngeal Mucosa Exam (NOME) Scores, Subject Symptom Self-Assessment (SSA) Rate, Investigator Assessment Findings (IAF)</td></tr>
<tr><td>Drug/Device Studied</td><td>Naloxone Nasal Spray 16mg/ml and 40mg/ml
Intramuscular/Intravenous injections of Naloxone

<table>
<tr><th>Study Arms</th><th>V1</th><th>V2</th><th>C3</th><th>C4</th></tr>
<tr><td colspan="5">Products</td></tr>
<tr><td>Drug Formulation Code*</td><td>N002-16-0.25</td><td>N002-40-0.25</td><td>Comparator</td><td>Comparator</td></tr>
<tr><td>Manufacturer</td><td>IMS</td><td>IMS</td><td>Hospira (ANDA 070256)</td><td>IMS (ANDA 072076)</td></tr>
<tr><td>Naloxone Concentration (mg/mL)</td><td>16</td><td>40</td><td>0.4</td><td>1</td></tr>
<tr><td>Fill Volume, mL</td><td>0.25</td><td>0.25</td><td>1</td><td>2</td></tr>
<tr><td colspan="5">Delivery</td></tr>
<tr><td>Delivery Route</td><td>IN</td><td>IN</td><td>IM</td><td>IV</td></tr>
<tr><td># of Nostrils for IN</td><td>1</td><td>1</td><td>-</td><td>-</td></tr>
<tr><td>Total volume delivered (mL)</td><td>0.25</td><td>0.25</td><td>1</td><td>2</td></tr>
<tr><td>Total Naloxone Dose (mg)</td><td>4</td><td>10</td><td>0.4</td><td>2</td></tr>
</table></td></tr>
<tr><td>Number and Type of Subjects</td><td>N=32
Healthy adult volunteers, male and female between the ages of 18 and 45 years old. The numbers of evaluable subjects are 25, 24, 27, and 26 for treatments V1, V2, C3, and C4, respectively. The gender profile of all treated subjects is 37.5% male and 62.5% female,</td></tr>
</table>

	with mean age (±S.D.) of 29.8 ± 6.4 years old, mean body weight 74.2 ± 13.8 kg, and mean height is 171.1 ± 9.6 cm.
Brief description of protocol	The study consisted of a screening visit, four (4) dosing visits separated by a 3 to 14 day period, and a follow-up phone evaluation 1 to 7 days after completion of the last visit. At each dosing visit, a total of 21 blood samples were collected at baseline, 1, 2, 3, 5, 10, 15, 18, 21, 24, 27, 30, 35, 40, 50, 60, 90, 120, 180, 240, and 360 minutes post-dose. Safety evaluations included assessment of vital signs, ECG, laboratory tests (CBC, metabolic panel, urinalysis), and adverse events.
Results	The formulation of the proposed N002 at different concentrations show a higher systemic exposure to the IM comparator during the early absorption phase. Both N002 products show an early onset suggesting that highly concentrated IN Naloxone is suitable for emergency use. There were a total of 13 Adverse Drug Events (ADEs) reported by 12 subjects in V1 (3), V2 (4), C3 (1), and C4 (5). All ADEs were mild (11/13) or moderate (2/13). 11/13 ADEs were not related to study drug treatments and 2/13 ADEs have an unknown relationship to study treatments.
Device Related Comments	There were no device-related comments included in the study summary.
Reviewer Comments	As part of the Mid-Cycle for this submission, an IR will be included requesting information on whether there were any device-related malfunctions or issues observed during the study. It is unclear whether the performance of the device was assessed as the device functionality was not included in the endpoints for the study.

Study Name	**A Randomized, Double-Blinded, Single-Dose, Two-Treatment, Two-Period, Crossover Study of Intranasal Naloxone HCl (N002) Effect on Olfactory**
Study Type	This was a randomized, double-blinded, two-treatment, crossover study conducted in healthy volunteers.
Objectives/Endpoints	This study aimed to evaluate effects of N002 (10mg in 0.25ml) on olfactory function in healthy adult volunteers. The olfactory function of study subject were evaluated using UPSIT (University of Pennsylvania Smell Identification Test). The assessment was compared between IN Naloxone and a placebo control in a crossover study. Primary Endpoint: Olfactory performance change from baseline Secondary Endpoint: UPSIT score change from baseline
Drug/Device Studied	Naloxone Nasal Spray 40mg/ml

	<table><tr><th>Study Treatments</th><th>P</th><th>T</th></tr><tr><td>Products</td><td></td><td></td></tr><tr><td>Drug Formulation Code*</td><td>N002-00-0.25</td><td>N002-40-0.25</td></tr><tr><td>Drug Product</td><td>Placebo</td><td>N002</td></tr><tr><td>Manufacturer</td><td>IMS</td><td>IMS</td></tr><tr><td>Naloxone Concentration, mg/mL</td><td>0</td><td>40</td></tr><tr><td>Fill Volume, mL</td><td>0.25</td><td>0.25</td></tr><tr><td>Delivery</td><td></td><td></td></tr><tr><td>Delivery Route</td><td>IN</td><td>IN</td></tr><tr><td>Dose, mg</td><td>0</td><td>10</td></tr><tr><td>Volume by IM, mL</td><td>-</td><td>-</td></tr><tr><td>Volume per Nostrils, mL</td><td>0.25</td><td>0.25</td></tr><tr><td># of Nostrils for IN</td><td>1</td><td>1</td></tr><tr><td>Total volume delivered, mL</td><td>0.25</td><td>0.25</td></tr><tr><td>Total Naloxone Dose</td><td>0 mg</td><td>10 mg</td></tr></table>
Number and Type of Subjects	N=28 Healthy adult volunteers, male and female between the ages of 18 and 45 years old. All 28 subjects had received both study treatments. The gender profile of all treated subjects is 42.9% (12/28) male and 57.1% (16/28) female, with mean age of 31.2 ± 8.5 years old, mean body weight 75.3 ± 14.3 kg, and mean height is 168.5 ± 9.0 cm.
Brief description of protocol	The study consisted of a screening visit, two (2) dosing visits separated by a 3 to 14 day period, and a follow-up phone evaluation 1 to 7 days after the completion of the last visit. At each study visit, the subject's olfactory function assessment were conducted using UPSIT evaluated at baseline and 4 hours post-dose. Safety evaluations included assessment of vital signs, ECG, laboratory tests (CBC, metabolic panel, urinalysis), and adverse events.
Results	The study demonstrates that there is no significant change in olfactory functions at the N002 strength tested.
Device Related Comments	There were no device-related comments included in the study summary.
Reviewer Comments	As part of the Mid-Cycle for this submission, an IR will be included requesting information on whether there were any device-related malfunctions or issues observed during the study. It is unclear whether the performance of the device was assessed as the device functionality was not included in the endpoints for the study.

Reviewer Comment
The Sponsor also included a retrospective study on the safety of dosing volumes greater than or equal to 0.25ml of IN medications in children 0 to 3 years of age using institutional databases and electronic medical records from hospitals/regional medical centers.

In the studies performed using the proposed product, the Sponsor has not indicated whether there were any device failures or whether/how device functionality was assessed.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION

Mid-Cycle Deficiencies: ☑ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Sponsor has resolved the below outstanding issues for the Naloxone Nasal Spray 4mg/0.25ml (16mg/ml).	
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No	

	Date Sent: 12/21/2022	Date/Sequence Received: 12/30/2022
Mid-Cycle Deficiency #8	(b) (4)	
Sponsor Response		
Reviewer Comments	The response is acceptable.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☑

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

(b) (4)

[redacted]

The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

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Reviewer Comments
The Sponsor provided a description and process flow charts of the assembly of the N002 Nasal Unit and the final finished combination product.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

12.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission: No

What Quality System did the Sponsor choose:
☐ Device QSR-based
☑ Drug cGMP-Based Streamline
☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): IMS	(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s): IMS	
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): IMS	
21 CFR 820.100 Summary of Corrective and	Firm(s): IMS	

Preventive Actions		

Reviewer Comments
The Sponsor has provided an overview of their 21 CFR 820 compliance.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

12.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

The following information was obtained from the document titled "3.2.R.1.P.2 Information on Components" in Module 3.2.R Regional Information of Sequence 0049.

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	Present
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	Y
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	Y
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	Y
Investigations into the cause of nonconformities relating to product, processes, and the quality system	Y
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	Y
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	Y
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	Y
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	Y
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	Y
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	Y
Requires documentation of all CAPA activities	Y

Reviewer Comments
The Sponsor has provided a high-level overview of their CAPA procedures. Additional information is needed and will be requested in the Mid-Cycle.

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.	☒Yes	☐No

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Pump Delivery (Spray Weight)	The Essential Performance Requirements (EPRs) outlined to the left are included in the Finished Product Specification for the Naloxone HCl Nasal Spray 4mg/0.25ml combination product.	Y
Spray Pattern		
Plume Geometry		
Droplet Size Distribution		
Spray Content Uniformity		
Actuation Force (Break/Glide Force)		

Reviewer Comments
The Essential Performance Requirement (EPR) control strategy is acceptable.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☑ Yes ☐ No ☐ N/A	☑ Yes ☐ No ☐ N/A	☐ Yes ☑ No ☐ N/A

Reviewer Comments
The Quality System documentation for Naloxone Nasal Spray 4mg/0.25ml (16mg/ml) is acceptable.

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent: 12/21/2022	Date/Sequence Received: 12/30/2022
Mid-Cycle Deficiency #9	(b) (4)	

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	(b) (4)
Reviewer Comments	The response is acceptable. The Sponsor also provided SOP documents in Sequence 0057 titled "Management Review Program", 'Corrective and Preventive Action (CAPA) Procedure", "Change Control System", and "Nonconformance Reporting" to support their response.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

<<END OF REVIEW>>

13.APPENDIX A **(INFORMATION REQUESTS)**

(b) (4)

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/s/

NAMRATA A THAKKAR
03/07/2023 04:48:16 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 22, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 208969
Product Name, Dosage Form, and Strength:	naloxone hydrochloride nasal spray device, 4 mg/0.25 mL
Applicant/Sponsor Name:	Amphastar Pharmaceuticals, Inc (Amphastar)
TTT ID #:	2022-1315-1
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, carton labeling, device peel lid (blister tray), and instructions for use (IFU) received on February 17, 2023 for naloxone hydrochloride. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label, carton labeling, device peel lid (blister tray), IFU, and PI for naloxone hydrochloride (Appendix A) to determine they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previoushuman factors results and label and labeling review.[a]

2 DISCUSSION

We note Amphastar clarified that they intend to use only numerical characters for the month and year of the expiration date in the proposed "YYYY-MM" format. Additionally, Amphastar added a horizontal linear barcode to the container label and indicated that the vertical barcode is a pharmacode used by Amphastar for internal use.

[a] Birkemeier D. Human Factors Results and Label and Labeling Review for naloxone hydrochloride (NDA 208969). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 FEB 8. TTT ID: 2022-1312 and 2022-1315.

3 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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02/22/2023 09:43:33 AM

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02/23/2023 09:23:38 AM

HUMAN FACTORS RESULTS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	February 8, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 208969
Product Name, Dosage Form, and Strength:	naloxone hydrochloride nasal spray device, 4 mg/0.25 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amphastar Pharmaceuticals, Inc (Amphastar)
FDA Received Date:	September 7, 2022
TTT ID #:	2022-1312 and 2022-1315
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Human Factors Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint MBA, PMP

1 REASON FOR REVIEW

This review evaluates a human factors (HF) validation study report, container label, carton labeling, device peel lid (blister tray), instructions for use (IFU), and prescribing information (PI) submitted under NDA 208969 for naloxone hydrochloride nasal spray.

1.1 PRODUCT DESCRIPTION

Naloxone hydrochloride nasal spray is a combination product with a proposed prefilled syringe (PFS) device constituent. Appendix A describes the relevant product information. Each nasal spray device is packaged individually in a blister tray, and each carton contains two blister trays. Appendix F provides images of the product and associated packaging elements.

1.2 REGULATORY HISTORY

NDA 208969 is a 505(b)(2) NDA and the listed drug product is Narcan, NDA 016636. Amphastar originally submitted NDA 208969 on April 19, 2016, which received a Complete Response (CR) on February 17, 2017, due to the following deficiencies[a]:

- Based on the results of the human factors validation study, the product user interface does not support a conclusion that all intended users can use this product safely and effectively. (b) (4) (b) (4)
- The design requirements specifications do not appear to contain requirements permitting (b) (4) as part of the spray characteristics, however, information provided described that the Delivery Amount includes (b) (4) .
- The proposed reliability specification at expiry of (b) (4)) is unacceptable for a product intended for emergency treatment of opioid overdose.
- Administration of the proposed volume of (b) (4) mL has the potential to lead to run-off into the posterior pharynx, especially in the youngest pediatric patients, raising safety concerns surrounding respiratory complications due to aspiration and effectiveness

[a] Kapoor S. Complete Response for naloxone hydrochloride. Silver Spring (MD): FDA, CDER, OND, DAAP (US); 2017 FEB 17. NDA 208969.

concerns due to inadequate absorption of naloxone. The pediatric assessment does not adequately address these concerns to support use of the product down to birth.

Thus, Amphastar submitted a Class 2 Resubmission on September 7, 2022. We note that the currently proposed product (4 mg naloxone nasal spray) differs in strength from the previously proposed product ((b) (4) naloxone nasal spray).

1.3 RELEVANT HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

We preliminarily reviewed summarized HF validation study results (Study #1 results) submitted in 2015 as a part of a meeting package for a Pre-NDA meeting. DMEPA identified task failures from the Study #1 results (b) (4) Based on our evaluation, we noted that these failures could have a negative impact on the product's efficacy. However, Amphastar did not provide adequate justification for why further risk mitigation strategies should not be employed. Based on the results, we provided comments to Amphastar on November 27, 2015, for their HF development program.[b]

In response to these comments, Amphastar subsequently completed and submitted results of a second HF validation study (Study #2), which we reviewed on January 17, 2017, during the first review cycle of NDA 208969. We note Amphastar did not submit a human factors validation study protocol for us to review prior to conducting Study #2. We concluded that the product user interface did not support a conclusion that all intended users can use the product safely and effectively. Thus, we recommended Amphastar re-evaluate the critical task failures and close calls, including their root causes, to implement additional risk mitigation strategies to prevent no dose or underdose, and demonstrate their effectiveness by conducting another HF validation study.[c] As described in Section 1.2 above, NDA 208969 subsequently received a CR on February 17, 2017.[d]

On June 14, 2017, we provided response to questions on the acceptable rate of failure in an HF validation study in a Type A End of Review Meeting (the meeting was held on May 15, 2017).[e]

On October 20, 2017, Amphastar submitted an HF validation study protocol under a Type A Meeting Request (Post-Action Meeting) under NDA 208969. Amphastar changed their device constituent part design to further mitigate the risk of an incomplete dose, and they revised the training plan for first responders based on our previous comments. This meeting was held on

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[b] Walker D. Meeting Minutes for naloxone hydrochloride. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2015 NOV 27. IND 124672.

[c] Schlick, J. Label and Labeling and Human Factors Results Review for naloxone hydrochloride. Silver Spring (MD): FDA, CDER, OSE, DAAP (US); 2017 JAN 17. NDA 208969.

[d] Kapoor S. Complete response for naloxone nasal spray. Silver Spring (MD): FDA, CDER, OND, DAAP (US); 2017 FEB 17. NDA 208969.

[e] Kapoor S. Type A End of Review Meeting Minutes for Naloxone Nasal Spray. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2017 JUN 14. NDA 208969.

November 28, 2017, and meeting minutes were issued on December 26, 2017. During this meeting, we agreed with Amphastar that an HF validation study is required for the proposed modified device design. Additionally, we requested Amphastar submit a formal request for feedback in a separate submission if they want a formal review of the human factors protocol. Amphastar agreed to conduct an HF validation study with the reconfigured device.[f] Thus, Amphastar formally resubmitted the same human factors protocol on December 6, 2017, under NDA 208969. We reviewed this HF protocol on January 16, 2018, and identified several areas of concern. Thus, we provided recommendations to Amphastar to implement before conducting their HF validation study.[g]

On March 18, 2020 (meeting minutes dated April 16, 2020), during a Type C Guidance Meeting, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine suggested Amphastar also consider including caregivers of young infants and infant mannequins to determine if the drug can be correctly administered to the infant mannequins to support approval in patients down to birth. Amphastar agreed to also include caregivers and infant mannequins. We also referred Amphastar to our guidances, and Amphastar agreed to submit an HF validation study protocol for review.[h]

Thus, on June 8, 2021, Amphastar submitted a human factors validation study protocol for Agency review under IND 124672. We completed our review of this HF validation study protocol on September 15, 2021, and provided recommendations to Amphastar to implement before conducting their human factors validation study.[i] The HF validation study results currently being reviewed are subsequent to the HF validation study protocol submitted June 8, 2021.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A

[f] Kapoor, S. Type A Follow-up to Post Action Meeting Minutes for Naloxone Nasal Spray. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2017 DEC 26. NDA 208969.

[g] Schlick J. Human Factors Protocol Review for naloxone hydrochloride (NDA 208969). Silver Spring (MD): FDA, CDER, OND, DAAP: (US); 2018 JAN 16. OSE RCM #: 2017-2502.

[h] Kapoor, S. Type C Guidance Meeting Minutes for Naloxone Hydrochloride Nasal Spray. Silver Spring (MD): FDA, CDER, OND, DAAMPM (US); 2020 APR 16. NDA 208969.

[i] Bhalodia A. Human Factors Validation Study Protocol Review for naloxone hydrochloride. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 15. OSE RCM # 2021-1161.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Human Factors Related Submission Documents	E
Labels and Labeling	F
N/A=not applicable for this review *We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance	

3 SUMMARY OF HUMAN FACTORS VALIDATION STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See *Human Factors Validation Study Results Report* (Appendix E) for full details.

Table 2. Study Methodology for Human Factors (HF) Validation Study

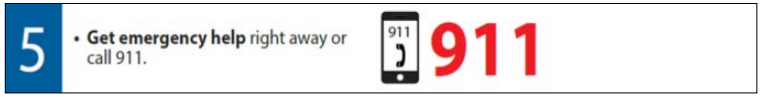
Study Design Elements	Details
Participants	<table><tr><th>User Group</th><th>Number of Participants</th></tr><tr><td>Adults aged 18-65 years old who may be in a position to administer a dose to a patient experiencing an emergency event. Included a mix of parents of younger children (3 years old and younger) and individuals without younger children. Also included a mix of individuals experienced in using nasal spray products and individuals who are naïve to nasal spray products.</td><td>15</td></tr><tr><td>Juveniles aged 10-17 years old. Included individuals with younger siblings (3 years old and younger) and individuals who do not have younger siblings. Also included a mix of individuals experienced in using nasal spray products and individuals who are naïve to nasal spray products.</td><td>15</td></tr><tr><td>First Responders aged 18-65 years old (e.g., school nurse, firefighter, paramedic, emergency medical technician, police officer, or emergency room nurse).</td><td>15</td></tr><tr><td>Total Overall</td><td>45</td></tr></table>
Training	None
Test Environment & Materials	Set up to simulate a home or public environment, including a table and chairs and a mannikin on the ground. For lay bystanders, product was on the ground inside a small pouch next to the mannikin. First responders walked into the room with the product. Half of the adult participants and half of the pediatric participants were assigned a human mannikin; the other half were assigned a one year old infant mannikin. The room included

	ambient sound simulating a public space or crowd played at a high level of ~75 db.
Sequence of Study	1. Untrained, unaided rescue trial a. Performance Task #1: Participant enters room and provides dose of naloxone to mannikin b. Performance Task #2: After participant completes first dose, moderator waits 2 minutes and instructs the participant to do what they would do next assuming the patient did not respond to the first dose. c. Post-Interaction Questions d. Error Debriefing 2. Knowledge Task Questions 3. Knowledge Task Questions Error Debriefing 4. Final Disposition and Subjective Feedback on whether participant thinks they could successfully administer a rescue dose with the device

4 RESULTS AND ANALYSES

4.1 SUMMARY OF HUMAN FACTORS VALIDATION STUDY RESULTS

We have carefully reviewed each observed event, Amphastar's URRA, the participants' subjective feedback, Amphastar's root cause analysis (RCA), and Amphastar's comments and proposed mitigations. For our analyses see Table 3 and Section 4.2 below.

	Table 3. Analysis of HF Study Results (All Tasks)	
	Legend: UE = use error; CC = close call; UD = use difficulty; URRA = use-related risk analysis; RCA = root cause analysis	
	Information Supplied by Amphastar	**DMEPA's Findings and Recommendations**
1.	Task: Get Emergency Help (Performance Task 1) Total Number of UE, CC, and UD: Use errors (n=1) Type of Participants: Adult – 1	
	Observed error(s): Participant did not get emergency help or call 9-1-1.	
	Risks associated with Task Errors (Per Amphastar's URRA): If this task is omitted or not performed correctly there is risk of: • Delay in further treatment • Partial or no symptom relief • Death	
	Relevant RCA/Subjective Feedback/Observation: • Internal decision (n=1): The participant stated he purposely skipped this step with the intention of getting emergency help after administering the second dose. Participant clearly processed the step, but purposely chose to skip the step and stated that no changes to the product could have prevented this action. Current Step 5 of the IFU:  Current Step 5 of the Blister Tray and Carton:	No identified concerns.

		
	Applicant Comment and Proposed Mitigations: None	Our review of the user interface and labels and labeling indicates that the IFU contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we find the residual risk acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
2.	Task: Insert nozzle into nostril, Dose into Opposite Nostril (Performance Task 2) Total Number of UE, CC, and UD: Type of Participants Use errors (n=4): Adult – 3, First Responder – 1	
	Observed error(s): Participants injected second dose into the same nostril as the first dose.	
	Risks associated with Task Errors (Per Amphastar's URRA): If this task is omitted or not performed correctly there is risk of: • Delay in further treatment • Partial or no symptom relief • Death	Per discussion with our Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) clinical colleagues, there is potential for decreased absorption of the second dose when administered into the same nostril as the first dose, which could lead to a decrease in efficacy.
	Relevant RCA/Subjective Feedback/Observation:	No identified concerns.

- One participant stated they thought the instructions were to just give another dose and they did not notice the instruction to use the opposite nostril. Using the opposite nostril was not clear. They stated they only read the first part of the instruction.
- One participant stated they thought it was the same nostril when the instructions said to "Repeat Steps 2, 3, and 4." so they went to repeat those steps without looking at the image in Step 7.
- One participant stated they did not see "opposite nostril" because they were focused on repeating steps 2-4.
- One first responder participant stated they gave the second dose in the same nostril because they thought that nostril looked bigger. They stated they were skimming the instructions because of the stress of the situation and focused on "Repeating steps 2-4." and they missed the instruction to use the opposite nostril.

Current Step 7 of the IFU:

(b) (4)

Current Step 7 of the Blister Tray and Carton:

	Applicant Comment and Proposed Mitigations: None Amphastar stated that "*the participants are focusing on the numbers within the first statement of step 7. If a user focuses on the numbers within the statement, they will read to give a 2nd dose and then focus on the reference for following steps 2-4. Participants missing this key information when the instruction is so salient within the image and instructions is an indication that users were likely skimming the steps of the IFU instead of reading and/or processing the illustrations.*"	Our review of the study results identified subjective feedback that indicated this use error was due to lack of salience understanding of the instruction in the IFU. One participant indicated that they focused on "give another dose" and stated that using the opposite nostril was not clear. Two adult participants and the first responder also indicated that the instructions state to repeat Steps 2, 3, and 4, and they missed the instruction to use the opposite nostril. Our review of the user interface and labels and labeling finds that Step 7 includes information to administer the second dose using a new device in the opposite nostril. However, based on our overall assessment, we find that the text can be improved to increase the saliency of the critical elements of administering the second dose (i.e., using a new device and administering into the opposite nostril). We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.

4.2 ANALYSIS OF OTHER TASK ERRORS

The HF validation study did not demonstrate use errors, use difficulties, or close calls with any tasks other than as described above in Table 3.

4.3 LABLES AND LABELING

Tables 4 and A below include the identified medication error issues with the submitted prescribing information, carton labeling, container labels, instructions for use, and device peel label, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

5 RECOMMENDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDITION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 4. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	In the *Dosage and Administration* section, the fourth bullet currently reads (b) (4) .	This bullet can be improved to provide greater clarity to the end user about how often they can administer additional doses.	We recommend revising this statement to read: "Administer additional doses of Naloxone Hydrochloride Nasal Spray using a new nasal spray device with each dose if the patient does not respond or responds and then relapses into respiratory depression. Additional doses of Naloxone Hydrochloride Nasal Spray may be given every 2 minutes until emergency medical assistance arrives. Note that similar changes are appropriate for Section 2 *Dosage and Administration* of the Full Prescribing Information.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented, emphasis is put on the concentration of the	Emphasis for this product should be placed on the strength and the dose that	Remove the information describing the product in terms of concentration, (b) (4)

Table 4. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	product (b) (4) rather than the total strength and dose provided by the device.	one device provides (i.e., 4 mg) to avoid confusion.	from Section 3 *Dosage Forms and Strengths*. This recommendation is also applicable to the *Dosage Forms and Strengths* section in the Highlights of Prescribing Information.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, emphasis is put on the concentration of the product (b) (4) rather than the strength and dose provided by the device. " (b) (4)	Emphasis for this product should be placed on the strength and the dose that one device provides (i.e., 4 mg) to avoid confusion.	We recommend revising this information to better reflect that each carton contains two individual blister trays sealed with a peel off feature, and that each blister tray contains one nasal spray device that administers a single dose of 4 mg. For example: (b) (4) "
2.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	Section 16 *How Supplied/Storage and Handling* should contain information suitable for product identification in accordance with 21 CFR 201.57(c)(17)(iii).	We recommend including identifying information in Section 16 *How Supplied/Storage and Handling* (e.g., add solution color and clarity information).

6 CONCLUSIONS AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors with a critical task that may result in harm. Based on our review of the available participants' subjective feedback,

Amphastar's root cause analysis and mitigation strategies, we identified additional risk mitigations to address the use errors. We have provided recommendations in Table A and Figure 1 for Amphastar.

Additionally, our review of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations in Table A and Figure 1 for Amphastar. We ask that the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) convey Table A and Figure 1 in their entirety to Amphastar. We advise these recommendations are implemented during this review cycle of NDA 208969. These changes can be implemented without submitting additional HF validation testing data for Agency review.

6.1 RECOMMENDATIONS FOR AMPHASTAR PHARMACEUTICALS, INC.

Our evaluation of the results of your human factors (HF) validation study, including participant subjective feedback and root cause analyses, indicates that there are additional labeling mitigations that can be implemented to address use errors that occurred with critical tasks. Additionally, our review of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations in Table A and Figure 1, and we recommend that you implement these recommendations and submit the revised labels and labeling for our review.

Table A. Identified Issues and Recommendations for Amphastar Pharmaceuticals, Inc (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the format of the expiration date is denoted as, "EXP: YYYY-MM". It is unclear if the month portion, "MM," of the expiration date format will use alphabetical or numerical characters.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug errors. For example, confusion has occurred with use of the alphabetical abbreviation "JU," which can represent both "June" and "July" and the alphabetical abbreviation "MA," which can represent both "March" and "May."	Clarify if you intend to use only numerical characters to express each portion of the expiration date.
Container Label			
1.	As currently presented, the container label contains the phrase "(b) (4)".	The intent of this statement is unclear. Additionally, the terminology "(b) (4) " is not consistent	We recommend revising this statement to read, for example, "Recommended

Table A. Identified Issues and Recommendations for Amphastar Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		with the terminology used in the labeling.	Dosage: See Prescribing Information. See Instructions for Use for Administration".
2.	As currently presented, the route of administration is not present on the container label.	Per 21 CFR 201.100(b)(3), the route of administration should be included on the container label and carton labeling.	Include the route of administration statement (e.g., For Use in the Nose Only) to help convey the intended route of administration. Additionally, consider removing one or both of the statements "NASAL Spray Device" to reserve space for critical label elements.
3.	As currently, presented, the packaging type term is listed as "(b) (4)".	The package type terminology is incorrect. Per USP <659> *Packaging and Storage Requirements*, the correct terminology for your product is "unit-dose".	Revise the package type term to read "unit-dose".
4.	As currently presented, it is unclear if the barcode on the container label is intended to be the linear barcode required per 21 CFR 201.25.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label.	Clarify if the current barcode is the linear barcode required by 21 CFR 201.25. If not, add the product's linear barcode to the container label as required per 21 CFR 201.25. Please note, the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode. Additionally, the barcode should be placed horizontally as opposed to vertically to facilitate scanning in an area where it will not be damaged.

Table A. Identified Issues and Recommendations for Amphastar Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling (see Figure 1 below for a detailed pictorial description of recommended changes)			
1.	As currently presented, the side panel of the carton labeling contains the recommended dosage statement, (b) (4) ".	The terminology (b) (4) is not consistent with the terminology used in the PI. Thus, this phrase can be improved for consistency with the PI. Additionally, regarding administration, the IFU includes more detailed administration instructions as compared to the PI.	We recommend revising the usual dosage statement to read, for example: "Recommended Dosage: See Prescribing Information See Instructions for Use for Administration".
2.	As currently presented, the strength statement reads (b) (4)	The strength statement lacks clarity that each device contains a 4 mg dose, which could lead to misinterpretation as both devices contain a total of 4 mg (e.g., 2 mg per device).	Revise the strength statement "(b) (4)" to read, for example, "4 mg per device" and remove the statement, (b) (4) Additionally, we recommend placing the strength statement immediately after the dosage form and before the route of administration.
3.	As currently presented, the route of administration is listed as (b) (4)".	This statement can be improved to increase consistency with the IFU.	Revise this statement to read "For Use in the Nose Only".
4.	As currently presented, the principal display panel (PDP) currently includes the concentration (b) (4)	The concentration statement "(b) (4) " could be misinterpreted as the total amount contained in each device.	Remove the statement, (b) (4)

Table A. Identified Issues and Recommendations for Amphastar Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	The side panel currently reads "(b) (4) "	The phrase "(b) (4)" could be misinterpreted as a strength of "(b) (4)".	For clarity and conciseness, we recommend revising and combining the statements to appear on the PDP. For example, revise to read "This box contains two (2) unit-dose 4 mg nasal spray devices".
6.	The PDP includes the net quantity statement "(b) (4) ".	The packaging type terminology "(b) (4)" is incorrect. Per USP <659> Packaging and Storage Requirements, the correct terminology for your product is "unit-dose". Additionally, we note discrepancy in how the product is described "device" versus "unit" across the labels and labeling.	
7.	As currently presented, the PDP contains the statement (b) (4) ".	This statement can be improved to increase consistency with the IFU.	Revise the statement to read "Use For Known or Suspected Opioid Overdose" and retain the statement "Seek Emergency Medical Attention".
8.	The PDP contains the statement (b) (4) ."	This statement can be improved to increase consistency with the IFU.	Revise this statement to read "See Instructions for Use for Administration".
9.	The PDP contains the phrase "(b) (4)	The packaging type terminology (b) (4)" is incorrect. Per USP <659> Packaging and Storage Requirements, the correct terminology for your product is "unit-dose".	Revise the phrase to read "(b) (4) ..." and relocate the phrase to the side panel to create space on the PDP.

Table A. Identified Issues and Recommendations for Amphastar Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Additionally, we note discrepancy in how the product is described "device" versus "unit" across the labels and labeling. Additionally, to maximize the prominence of critical product information, statements such as the [redacted (b) (4)]" statement should be located on the side panel. See *our Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to minimize Medication Errors* for more information.[j]	
Device Peel Label (Blister Tray Label) (Please note these recommendations additionally apply to the image on the side panel of the carton labeling)			
1.	As currently presented, the device peel label reads "[redacted (b) (4)]	This statement can be improved to increase consistency with the IFU.	Revise this statement to read "Refer to Full Instructions for Use."
2.	As currently presented, the route of administration is listed as "[redacted (b) (4)]".	This statement can be improved to increase consistency with the IFU.	Revise this statement to read "For Use in the Nose Only".
3.	As currently presented, the strength statement	The current presentation of the strength statement	Revise the strength statement to read "4 mg per device" and

[j] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to minimize Medication Errors. 2022. Available from: https://www.fda.gov/media/158522/download.

Table A. Identified Issues and Recommendations for Amphastar Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	reads "(b) (4) ".	could lead to confusion and medication dosing errors.	remove (b) (4)
4.	As currently presented, step #7 (b) (4) when administering a second dose.	This information is critical for the end user. If the end user does not use a new device, this could result in a delay of treatment, or no dose being given.	Revise the phrase "If no response, give 2nd dose" to "If no response, give 2nd dose with new device".
Instructions for Use			
1.	Step 7 can be improved to increase the saliency of the critical elements of administering the second dose (i.e., using a new device and administering into the opposite nostril).	Per the URRA, if the users do not correctly dose into the opposite nostril there is risk for reduced efficacy, partial or no symptom relief, and death. The human factors validation study identified subjective feedback that participants focused on the part of the instructions that state to repeat Steps 2, 3, and 4, and they missed the instruction to use the opposite nostril. Participants also indicated that lack of salience was a contributing factor.	We recommend revising the text on the left side of Step 7 to increase saliency of the critical elements of administering the second dose (i.e., using a new device and administering into the opposite nostril). For example, this could be done by means of bolding, using a different font color, highlighting, etc.: (b) (4)
2.	We note the IFU does not instruct the end user to place the person in the recovery position.	Generally, it is recommended to move the person into the recovery position after administration of naloxone. The recovery position is a common first aid practice that is performed when a person is unconscious but breathing and has no other	We recommend revising step 7 to include instruction to place the person in the recovery position. For example, include an additional bullet to convey this information: • If no response, give a 2nd dose with a new naloxone NASAL Spray device in the opposite nostril following

Table A. Identified Issues and Recommendations for Amphastar Pharmaceuticals, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		life-threatening conditions. The recovery position helps to keep the airway clear and open and ensures that any vomit or fluid will not create a choking hazard.	the instructions in steps 2 to 4 above. • If the person responds by waking up, to voice or touch, or starts breathing normally, place the person on their side (recovery position). • Watch the person until emergency help arrives. Additionally, we recommend including an image to depict the recovery position.
3.	The PDP contains the statement (b) (4)	The packaging type terminology "(b) (4)" is incorrect. Per USP <659> Packaging and Storage Requirements, the correct terminology for your product is "unit-dose". Additionally, we note discrepancy in how the product is described "device" versus "unit" across the labels and labeling.	Revise the phrase to read "Each unit-dose NASAL spray device contains…" and relocate the phrase to the side panel.

Figure 1. Detailed Description of Carton Labeling Recommendations

Amphastar Proposed Carton Labeling	Agency Recommended Carton Labeling Changes
(b) (4)	
*Note that Font Style/Sizes and Spacing may be edited at Amphastar's discretion	

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for naloxone hydrochloride that Amphastar Pharmaceuticals, Inc submitted on October 31, 2022, and the listed drug (LD).

Table 5. Relevant Product Information for Listed Drug and naloxone hydrochloride		
Product Name	Narcan	Naloxone hydrochloride
Application Type and Number	NDA 016636	NDA 208969
Initial Approval Date	April 13, 1971 (withdrawn FR effective on August 20, 2010)	n/a
Active Ingredient	Naloxone	Naloxone
Indication	Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine. Also indicated for diagnosis of suspected or known acute opioid overdosage.	(b) (4)
Route of Administration	Intravenous, intramuscular, or subcutaneous	intranasal
Dosage Form	Injection	Nasal spray
Strength	• 4 mg/10 mL (0.4 mg/mL) • 10 mg/10 mL (1 mg/mL) • 0.04 mg/2 mL (0.02 mg/mL) • 0.4 mg/mL • 2 mg/2 mL (1 mg/mL)	4 mg/0.25 mL
Dose and Frequency	<u>Intravenous Infusion:</u> • May be diluted for intravenous infusion in normal saline or 5% dextrose. Addition of 2 mg of Narcan in 500 mL	Recommended initial dose in adults and pediatric patients is the contents of one device (4 mg) delivered by intranasal administration. Seek emergency medical assistance as soon as possible after

	provides a concentration of 0.004 mg/mL. Use solution within 24 hours. The rate of administration should be titrated in accordance with the patient's response. General: • Usage in Adults: o Opioid Overdose (Known or Suspected): Initial dose of 0.4 to 2 mg administered intravenously. May repeat dose at 2-3 minute intervals. If no response observed after 10 mg has been administered, question the diagnosis. May administer intramuscularly or subcutaneously if intravenous route is not available. o Postoperative Opioid Depression: Titrate dose to response. For initial reversal of opioid depression, inject in increments of 0.1 mg to 0.2 mg intravenously at 2-3 minute intervals to desired level of reversal. • Usage in Children: o Opioid Overdose (Known or Suspected): usual initial dose is 0.01 mg/kg given intravenously. May	administering. The requirement for repeat doses of naloxone depends upon the amount, type, and route of administration of the opioid being antagonized. Administer in alternate nostrils with each dose. If the patient responds and relapses back into respiratory depression before emergency assistance arrives, administer an additional dose of naloxone using a new nasal spray device. If desired response is not obtained after 2 minutes, administer an additional dose using a new nasal spray device.

	administer an additional dose if necessary. May give subcutaneously or intramuscularly if intravenous route is not available. o Postoperative Opioid Depression: For initial reversal, inject in increments of 0.005 mg to 0.01 mg intravenously at 2-3 minute intervals to desired degree of reversal. • Neonates: o Opioid-induced Depression: usual initial dose is 0.01 mg/kg administered intravenously, intramuscularly, or subcutaneously. May repeat as needed.	
How Supplied	• 4 mg/10 mL (0.4 mg/mL) multiple dose vial – box of 1 • 10 mg/10 mL (1 mg/mL) multiple dose vial – box one 1 • 0.04 mg/2 mL (0.02 mg/mL) unit dose ampule – box of 10 • 0.4 mg/mL unit dose ampule – box of 10 • 2 mg/2 mL (1 mg/mL) unit dose ampule – box of 10	Carton containing two single dose nasal spray devices (prefilled syringes). Each nasal spray device comes in an individual tray.
Storage	Store at 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Protect from	Store naloxone hydrochloride nasal spray in the blister and cartons provided. Store at controlled room temperature 68°F to 77°F (20°C to 25°C).

	light. Store in carton until contents have been used.	Excursions permitted between 39°F to 104°F (4°C to 40°C). Do not freeze. Protect from light.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 2, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms NDA 208969. Our search identified two previous reviews[k,l] and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX E. HUMAN FACTORS RELATED SUBMISSION DOCUMENTS

- The HF validation study results report is accessible in EDR via: \\CDSESUB1\EVSPROD\nda208969\0049\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\n002-hf-study\human-factors-val-study-report.pdf
- The HF validation study protocol is accessible in EDR via: \\CDSESUB1\EVSPROD\nda208969\0049\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\n002-hf-study\human-factors-val-study-protocol.pdf
    - Note the URRA is available beginning on page 31 of the HF validation study protocol

[k] Schlick J. Label and Labeling and Human Factors Results Review for naloxone hydrochloride (NDA 208969). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 17. OSE RCM No.: 2016-963 and 2016-964.

[l] Schlick J. Human Factors Protocol Review for naloxone hydrochloride (NDA 208969). Silver Spring (MD): FDA, CDER, OND, DAAP: (US); 2018 JAN 16. OSE RCM #: 2017-2502.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[m] along with postmarket medication error data, we reviewed the following naloxone hydrochloride labels and labeling submitted by Amphastar Pharmaceuticals, Inc. on September 7, 2022, and on October 31, 2022.

- Container Label
- Device Peel Lid Labeling
- Carton Labeling
- Instructions for Use
- Prescribing Information (Image not shown), comparing the previously submitted labeling to the currently proposed labeling, available from \\CDSESUB1\EVSPROD\nda208969\0049\m1\us\draft-labeling-text-pdf.pdf;
- Prescribing Information (Image not shown) comparing the currently proposed labeling to the RLD (Narcan) labeling, available from \\CDSESUB1\EVSPROD\nda208969\0052\m1\us\package-insert-comparison.pdf

F.2 Label and Labeling Images

Container Label

[m] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

6 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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JASON A FLINT
02/09/2023 08:23:31 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Ndidi Nwokorie, MD Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)

Subject: Adequacy of 0.25 mL intranasal volume for pediatric use down to birth

Applicant: Amphastar Pharmaceuticals, Inc.

Application number: NDA 208969

Drug: Naloxone Nasal Spray

Drug Class: Opiate Antagonist

Proposed Indication:

- For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
- Naloxone Hydrochloride Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present.

Proposed Dosage: 1 spray intranasally into one nostril. Additional doses may be given every 2-3 minutes until emergency medical assistance arrives.

Route of administration: Intranasal (IN)

Dosage Form: Single dose solution in a pre-assembled IN injector

Dosage Strengths: 4 mg/spray

Materials Reviewed:

The following documents entered into DARRTS under NDA 208969

- DPMH Memorandum - (b) (4) dated January 19, 2017
- Complete Response (CR) Letter dated February 17, 2017
- Type A Meeting Minutes dated December 26, 2017
- Type C Meeting Minutes dated April 16, 2020
- Division of Pediatric and Maternal Health Consult Request dated October 6, 2022
- DPMH Memorandum dated October 30, 2018
- Division of Applied Regulatory Science (DARS)Memorandum dated January 25, 2023

Documents submitted to DocuBridge under NDA 208969

On September 7, 2022

- Complete Response to CR Letter
- Clinical Study Report of Study N002-CL-C
- Summary Report - Computational Fluid Dynamics Simulations

On April 19, 2016

- Agreed Initial Pediatric Study Plan

Consult Request:

DAAP consulted DPMH to opine on the adequacy of the 0.25 mL IN volume for administration to pediatric patients from birth to 3 years of age.

I. Relevant Pediatric Regulatory Background

Amphastar Pharmaceuticals, Inc.[1] submitted an initial new drug application (NDA) in 2016 seeking approval for naloxone hydrochloride nasal spray in all populations for immediate use by prescription as emergency therapy for the complete or partial reversal of opioid depression, including respiratory depression, in both outpatient and community settings where opioids may be present. The NDA was submitted under the 505(b)(2) pathway and relied on FDA's previous findings of efficacy and safety for Narcan for injection (NDA 016636) as the listed drug. The NDA included pivotal data from two comparative bioavailability studies conducted in healthy adult volunteers 18 to 45 years of age to demonstrate that Naloxone Hydrochloride Nasal Spray achieves comparable or higher systemic exposure and comparable or quicker onset of action compared to an approved dose and route of administration for naloxone HCl (e.g., intramuscular injection of 0.4 mg naloxone). The pediatric assessment consisted of the Applicant's review of the published literature and published practice guidelines to justify use of a fixed (b) (4) dose of Naloxone Hydrochloride Nasal Spray in all pediatric ages. The Applicant also leveraged pediatric use information from the approved labeling of the listed drug to support the safety and efficacy of Naloxone Hydrochloride Nasal Spray in all pediatric ages.

DAAP issued a Complete Response (CR) on 2/17/2017[2]. Although Naloxone Hydrochloride Nasal Spray met DAAP's pharmacokinetic (PK) standard for approval of novel naloxone drug products, failures by untrained laypersons to use the product correctly in the Human Factors Validation Study raised concerns by the review team that failure to deliver the effective dose due to (b) (4) inadequate IN delivery would lead to an unfavorable risk benefit profile not only in adults but also in pediatric patients requiring an effective naloxone dose as life-saving treatment in an emergency setting. (b) (4) of the product has the potential to result in treatment failure from inadequate delivery of the full intended IN dose.

Another deficiency conveyed in the CR letter pertained to insufficient information included in the NDA to address the safety of administering the (b) (4) volume, (b) (4) to patients down to birth. The Applicant cited multiple references to support the safe and effective use of the proposed (b) (4) volume, but the referenced publications were either general reviews of IN drug delivery or were published studies supporting the successful use of other IN drugs for seizure control, acute pain control, and pre- and intra-procedure sedation; none of the drugs were FDA approved for IN use in pediatric patients for the described indications. DPMH concluded during the first cycle of the NDA review that the pediatric assessment did not adequately address the potential safety concerns associated with this

[1] Hereafter referred to as Amphastar or "the Applicant"

[2] Complete Response Letter dated February 17, 2017

[redacted] volume to support use down to birth. Because pediatric studies to assess the safety of the proposed IN volume for the proposed indication are challenging to conduct from both an ethical and feasibility perspective, DPMH recommended the Applicant consider re-formulating the product [redacted] to ensure the product can be safely used in adults and pediatric patients down to birth.

DAAP granted a Type A Meeting Request and met with the Applicant in November 2017 to discuss the deficiencies outlined in the CR letter and to gain agreement on a path forward for the regulatory approval of the product.[3] In one of the questions, the Applicant sought DAAP's agreement on the proposed [redacted] 0.25 mL for use down to birth. The following key points were discussed:

- The Division disagreed and strongly encouraged the Applicant to reformulate the product [redacted]
- The Division agreed to accept additional published data from use of products delivering IN volumes greater than 0.25 mL in hospital settings but noted that, whether these data could support the pediatric safety of a 0.25 mL IN volume would be a review issue.
- The Division noted that the adult PK study results had shown that IN naloxone administration [redacted] resulted in different naloxone exposures than when administered [redacted]. DAAP told the Applicant it must address the relevance of this difference in the pediatric population.
- The Division expressed concern with the high IN volume resulting in runoff, inadequate dosing, and aspiration. The Division also expressed concern about loss of efficacy from inadvertent swallowing of IN naloxone because of its poor oral bioavailability.
- The Division advised the Applicant to provide any data, specifically safety information, related to experiences with off-label use of higher IN volumes in pediatric patients to help support the proposed 0.25 mL IN volume of this product.

The Division granted a Type C Meeting Request and met with the Applicant in March 2020 to discuss the pediatric and human factors engineering study plans for the proposed product.[4] The meeting included the following discussion on the acceptability of the 0.25 mL IN volume:

- The Division agreed that the Applicant's proposal was reasonable to rely on three analyses included in the meeting package to support its claims that the 0.25 mL IN volume is safe and does not pose efficacy concerns due to run-off and consistent with prior advice given by the Division. The analyses included: (1) a retrospective analysis of documented adverse events from patient encounters in electronic medical records (EMR) databases of hospitalized pediatric patients undergoing procedural sedation with IN drug products; (2) static study and computational simulation model of nasal passages based on computed tomography (CT) images from a 10 day old neonate and a 3 year old child to inform the

[3] Meeting Minutes entered into DARRTS under NDA 208969 on 12/26/17.

[4] Meeting minutes entered into DARRTS under NDA 208969 on 4/16/20.

amount of product expected to remain within the nasal cavity after IN administration; (3) human factors validation testing to include caregivers of young infants and infant mannequins to determine if the drug can be correctly administered to the infant mannequins.

- The Division advised the Applicant that an NDA resubmission should include further characterization of the demographics, underlying comorbidities, and use of concomitant medications in the retrospective analysis.
- The Division advised the Applicant to provide a composite of multiple scans of patients, not limited to a single neonate and 3-year-old child, to provide greater confidence that volume estimates simulated by the computational nose model study would be representative of the age being analyzed. DAAP and the Applicant agreed that the model would include pediatric patients who were ages 10 days, 1 month, 3 month, 6 months, and 1 year.

FDA received a Class 2 resubmission of NDA 208969 on 09/07/2022. The NDA resubmission is subject to a Priority Review with a PDUFA goal date of March 7, 2023.

The resubmission includes the following new data:

- Results from a physiology-based, in silico modeling study performed using the computational fluid dynamics (CFD) software ANSYS Fluent.[5] The purpose of this study was to determine whether a run-off into the posterior pharynx or further into throat occurs and quantify the run-off volume in pediatric patients when using naloxone nasal spray liquid solution by simulation. The modeling focused on the airway of children less than 3 years of age. The Division of Applied Research and Science (DARS) reviewed this study. The model was found to address the variability in pediatric nasal anatomy and the proposed IN volume to be consistent with published clinical practice. However, there was discrepancy noted between the predicted run-off from the model and that described in the literature[6] for the 0.5 mL volume for a 3-year-old airway model. (0.1% vs 30%) This discrepancy may be due to differences in the study conditions (droplet size distribution, spray plume angle, droplet release velocity, liquid density and viscosity, and head position). To decrease the prediction uncertainty and increase the credibility of the minimal run-off prediction of 0.25 mL of the Applicant model, DAAP requested the Applicant either provide valid justification for the discrepancy or conduct the simulation using the same parameters found in the literature for comparison.[7] The Applicant complied and, using previous in vitro administration parameters, predicted a run-off of 25%, which was comparable to the in vitro measured value of 30% included in the publication. The ability of the Applicants 3D computational

[5] Summary Report- Computational Fluid Dynamics Simulations submitted to DocuBridge on 9/7/2022

[6] Hosseni et al. In vitro measurement of regional nasal drug delivery with flonase, flonase sensimist, and mad nasal in anatomically correct nasal airway replicas of pediatric and adult human subjects. Journal of Aerosol Medicine and Pulmonary Drug Delivery. (2019) 32:374

[7] DARS Consult Response -NDA 208969 MS Study Report Final in DARRTS 1-25-2023

model to generate comparable results to external, independent experimental results increases the credibility of their model and DARS' confidence in the predicted run-off.[8]

- Human factors validation testing study conducted for the redesigned device in the following user groups: (1) adult users; (2) juvenile users 10 years of age and older; and (3) first responders. DPMH defers to the Division of Medication Error Prevention and Analysis (DMEPA) on the adequacy of these studies.
- Safety analyses of electronic medical records (EMRs) from four inpatient settings of adverse outcomes related to IN drug administration to hospitalized patients from birth to less than 3 years of age.

This memorandum focuses on DPMH's assessment of the retrospective safety analyses included in the resubmission to support the safety of the new proposed 0.25 mL IN volume for pediatric use down to birth.

II. DPMH Discussion of Applicant's Safety Analysis of 0.25 mL IN Volume Using EMRs

The Applicant provided results from two analyses focused on the safety of IN drugs at volumes of 0.25 mL or more that were administered for sedation, analgesia, or both to hospitalized pediatric patients less than 3 years of age. The Applicant conducted the first analysis in 2019 and focused on safety data retrieved from EMR databases from 2 tertiary care teaching hospitals and 2 regional hospitals in the United States. The primary objective was to determine the incidence of aspiration, if any, that resulted due to IN dosing volume in patients who had received an IN drug at the dosage defined by the hospitals' standardized IN dosing procedures and protocols. The primary outcome was the incidence of adverse events (AE) related to IN dosing volume, specifically defined as respiratory compromise such as signs and symptoms of aspiration. The Applicant repeated the analysis, one year later in 2020, using data retrieved from the same sources and combined the data with that retrieved from 2019 to provide a pooled analysis of the primary outcome. The Investigators collected 25-item patient data (Appendix 1), when available, grouped into four (4) categories from the 4 pediatric centers.

The pooled analysis incorporated prior advice conveyed by the Division to the Applicant[4] and provided additional demographic details, underlying comorbidities, and use of concomitant medications about the pediatric population analyzed. After excluding patients who had received IN volumes less than 0.25 mL, the Applicant identified a combined total of 571 cases in 562 patients ranging in age from 3 days to 36 months; 6.6% of the population was less than 1 year of age. The administered IN volumes ranged from 0.25 mL to 3.9 mL (mean of 0.87 mL), Table 4; and the mean IN volume administered to those less than 1 year of age was 0.61 mL. The Applicant did not provide the range of IN volumes administered to those less than 1 year of age, Table 5.

[8] Email communication from Dr. Zhihua Li February 2, 2023

Table 4: Range of IN Delivery Volume in Patients from Birth to Less than 3 Years

Range of IN Delivery Volumes	Number of Cases	Percent Total Cases
0.25 to 0.30 mL	71	12.4%
0.31 to 0.50 mL	55	9.6%
0.51 to 1.00 mL	307	53.8%
1.10 to 3.90 mL	138	24.2%

Source: Adapted by this reviewer from Clinical Study Report of Study N002-CL-C

Table 5: IN Medication Dosing Volume by Age Group

Pediatric Age Range (years)	No. in Cohort	Average Dosing Volume (mL)
0-1	37	0.61
1-2	260	0.77
2-3	274	1.00

Source: Adapted by this reviewer from Clinical Study Report of Study N002-CL-C

The investigators analyzed data for clinical signs of aspiration that included the following:

- Coughing
- Wheezing
- Fever
- Chest discomfort
- Pulmonary edema
- Signs of progression into severe respiratory distress

The timeframe within which patients were observed for these clinical signs was not included in the submission. The Applicant appeared to target immediate signs of aspiration during the procedure but also reviewed records for any signs likely to manifest post-procedure such as fever and progression to respiratory distress.

They report that there were no signs suggestive of aspiration. Six AEs were captured, but none were serious. One AE described oxygen desaturation, but the Applicant did not provide any additional details or clinical context to help determine if this AE was attributed to the sedative effect of the drug administered or the IN administration itself. Per the Applicant, this AE resolved spontaneously and quickly without further need for intervention. Comorbidities were consistent with those expected in a general pediatric population and included the following:

- Food allergies (3%)
- Prematurity (3%)
- Eczema (2%)
- Bronchial hyperactivity (2%)

These comorbidities do not appear to have impacted the safety assessment because there were no reports of AEs related to airway irritability, the most likely AEs expected with these underlying conditions. The most frequently reported concomitant medications included midazolam, epinephrine/lidocaine/tetracaine (LET), acetaminophen, ibuprofen, and lidocaine. None of these concomitant medications would be expected to confound the safety assessment.

III. Conclusion

Amphastar's analyses of EMRs from 4 US hospital settings included an adequate number of patients representative of the age range from birth to less than 3 years and did not identify any SAEs attributed to the IN administration of drugs in volumes ranging from 0.25 mL to 3.9 mL. These findings are supportive of the pediatric safety of the 0.25 mL IN spray volume in the youngest patients. There are currently no approved IN drug products with volumes greater than 0.125 mL.

IV. Appendix: 25-Item Patient Data Collection List

Items for Data Collection	Description
Group-1 Study Site Information:	
1) Case No (generated by Institution)	
2) Name of Hospital Medical Center	
3) Provider Specialty or Clinic	Emergency Department, Anesthesiology or Others
4) Location	City and State
Group-2 Patient Information:	
5) Gender	
6) Year of Intervention	
7) Age at the time of IN Treatment (months)	
8) Weight (Kg)	
9) Height (cm)	
10) Race (Asian, African-American, Caucasian, Pacific Islander, American Indian/Native, Others)	
11) Ethnicity (Hispanic or Latino, Y/N)	
12) Concomitant Medications	

13) Comorbidities (if any, documented in medical history)	
Group-3 IN Medication and Treatment Information:	
14) Indication for IN Intervention	
15) Hospital Protocol or Dosing Chart Used	Y/N
16) Name of IN Medication(s) Received	
17) Concentration of IN Medication Used (mg/mL)	
18) Dosing Volume per Nostril (mL)	
19) Number of Nostril(s) Dosed	
20) Total dose of IN medication (mg)	
21) States of consciousness prior to IN intervention	Asleep/Unconscious, Drowsy, or Alert
Group-4 Post-Treatment Information:	
22) Adverse Event (AE)?	Y/N, if Y, classified AE per MedDRA Preferred Terminology
23) Did aspiration occur during or after IN dosing?	Y/N
24) Was it a Serious Adverse Event (SAE) related to IN delivery?	Y/N
25) Notes/Comments	

Source: Study Report NOO2-CL-C

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JOHN J ALEXANDER
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 2, 2023

To: Corinee Ahmar, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Namrata Thakkar, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for Naloxone Hydrochloride Nasal Spray

NDA: NDA 208969

In response to DAAP's consult request dated October 21, 2022, OPDP has reviewed the proposed product labeling (PI), Patient Package Insert (PPI)/Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Naloxone Hydrochloride Nasal Spray**.**

PI/PPI/Medication Guide/IFU: OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 19, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide/IFU, and comments were sent under separate cover on January 31, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on September 7, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

19 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 31, 2023
To:	Namrata Thakkar, PharmD, BCPS Regulatory Project Manager **Division of Anesthesiology, Addiction, Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Sheneé Toombs, PharmD, CPH Senior Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name), Dosage Form and Route:	Naloxone Hydrochloride Nasal Spray
Application Type/Number:	NDA 208969
Applicant:	Amphastar Pharmaceuticals, Inc.

1 INTRODUCTION

On September 7, 2022, Amphastar Pharmaceuticals, Inc. submitted for the Agency's review a Class II resubmission for their original New Drug Application (NDA) 208969 for Naloxone Hydrochloride Nasal Spray, in response to a Complete Response (CR) letter dated February 17, 2017. The Reference Listed Drug (RLD) is NARCAN (Naloxone Hydrochloride Injection, USP) NDA 016636. (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction, Medicine, and Pain Medicine (DAAP) on October 21, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Naloxone Hydrochloride Nasal Spray.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft Naloxone Hydrochloride Nasal Spray PPI and IFU received on September 7, 2022, and received by DMPP and OPDP on January 19, 2023.
- Draft Naloxone Hydrochloride Nasal Spray Prescribing Information (PI) received on September 7, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 19, 2023.
- Approved NARCAN (naloxone hydrochloride) nasal spray comparator labeling dated August 6, 2020.
- Approved KLOXXADO (naloxone hydrochloride) nasal spray comparator labeling dated April 29, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

8 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

RUTH I MAYROSH
01/31/2023 11:55:43 AM

LATOYA S TOOMBS
01/31/2023 02:12:01 PM

LASHAWN M GRIFFITHS
01/31/2023 02:21:22 PM

Date: January 23, 2023

From: Zhihua Li, PhD, Division of Applied Regulatory Science (DARS), Office of Clinical Pharmacology (OCP)

Through: Rebecca Racz, PharmD, DARS Consult Lead, and Jeff Florian, PhD, DARS Associate Director

To: Corinne Ahmar, Silvana Borges, and Namrata Thakkar, OND

Subject: Input regarding a modeling and simulation study report submitted on 1/6/23

Executive Summary

This consult request was to evaluate the sponsor's report combining ex vivo data and computational simulation using age-dependent nose-throat airway models to assess the run-off volumes of their nasal naloxone product.

This is a more detailed and updated version of a report submitted by the sponsor in 2019. DARS previously reviewed the 2019 report and raised a concern that the model was (b) (4)

This may ignore the variability in pediatric nasal airway anatomy and underestimate the uncertainty of modeling results. In the new report, the sponsor expanded the number of models to six pediatrics, with five of them younger than 1 year old. The results demonstrated age-dependent inter- and intra- subject variability and addressed DARS's original concern.

The sponsor predicted the run-off fractions from different nasal spray volumes and concluded that with the product's intended spray volume of 0.25 mL, there is minimal (~1%) run-off, even when the spray volume was administered to neonates. The intended spray volume of 0.25 mL seems to be within the pediatric nasal administration volume ranges recommended and used by clinicians in literature. However, there is a ~30% difference between the sponsor's computational model and measured run-off fraction of high (0.5 mL) nasal spray volumes from in vitro pediatric models in the literature. Explaining such a discrepancy could significantly decrease the prediction uncertainty and increase the creditability of the sponsor's model. A recommendation to the sponsor was provided according to this evaluation.

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Background

The sponsor of this NDA previously submitted a computational fluid dynamics simulation for their intranasal (IN) naloxone product to support their claim that there is negligible run-off volume of their IN spray (administration volume of 0.25 mL) in pediatric subjects. The run-off volume is defined as the portion of sprayed product reaching the pharynx and beyond, and not available for immediate absorption. Consulted by the review division, DARS reviewed that 2019 report and raised a concern that pediatric internal nasal anatomy is highly variable. As the sponsor performed the simulation using nose-throat geometry models based on the Computed Tomography (CT) scan images of a single 10-day-old subject and a single 3-year-old subject, DARS comments that the sponsor's data and models did not appear to be sufficient to provide a clear understanding of the population structure and variability. DARS recommend the sponsor conduct additional modeling assessments to provide to have a more representative population and to better understand sensitivity around the computational model.

In 2023, a new modeling report was submitted by the sponsor. Some of the new investigations were conducted in response to the concern and suggestions raised by DARS. This document contains DARS' evaluation of the new modeling report.

Evaluation

Brief summary of the sponsor's methodology and results

After IN administration, deposited droplets tend to form a thin-layer liquid film on the mucosa. However, there is a maximally allowed liquid film thickness (ALFT), beyond which the extra liquid may run off. For a given small area (termed as the "surface element") on the nasal mucosa, ALFT depends on the tilt angle (theta) between the element and the ground. The sponsor performed an ex vivo static study on suckling pig nasal mucosa to determine the relationship between theta and ALFT.

As a second step, based on CT scan images, nose-throat geometry models for a series of ages were constructed. Each geometry model was divided into millions of surface elements (mesh). Assuming the whole head is in a supine position, the tilt angle (theta) between each surface element and the ground was determined. Additionally, the ALFT of each surface element within the nose-throat model was established by using the data from the ex vivo pig study above.

Finally, a computational fluid dynamics model was used to simulate the spray of the product, the droplet formation, transportation and deposition, as well as liquid film development. The simulation used some product-specific parameters such as droplet size and release velocity (based on imaging), and liquid density and viscosity. The ALFT established for each surface element was used to simulate film development and liquid run-off for each small area. The liquid film formed in three anatomical regions is considered available for absorption: (i) vestibule and valve (V&V), (ii) turbinate (TR), and (iii) nasopharynx (NP). The liquid reaching the furthest (iv) anatomical region pharynx and beyond is considered run-off.

The modeling results suggested that, despite some inter-subject variability, the 10-day-old model has the largest run-off fraction due to its smaller nasal airway volume compared to other older-age models. For the

10-day-old model, a spray volume of (b) (4) µL (the intended dosing volume) resulted in only ~1% run-off. For a spray volume of (b) (4) µL, which is the highest possible deliverable volume from the device due to the manufacturing variability when (b) (4) µL was intended, the run-off fraction was less than 3%. Based on these observations, the sponsor claimed that the risk resulting from medication runoff in nasal airways was minimal for their product in neonates or pediatrics less than 1 years of age.

DARS' evaluation

Does the model consider the variability of pediatric nasal anatomy?

In the original consult document, DARS raised a concern that internal nasal anatomy is highly variable, and the sponsor's usage of CT scan images of a single 10-day-old subject and a single 3-year-old subject to construct the nose-throat geometry models may be insufficient to reflect population variability.

In the new report, the sponsor expanded the number of nose-throat geometry models from 2 to 6 pediatrics. Now it includes:
1) 10-day-old female model
2) 3-year-old female model

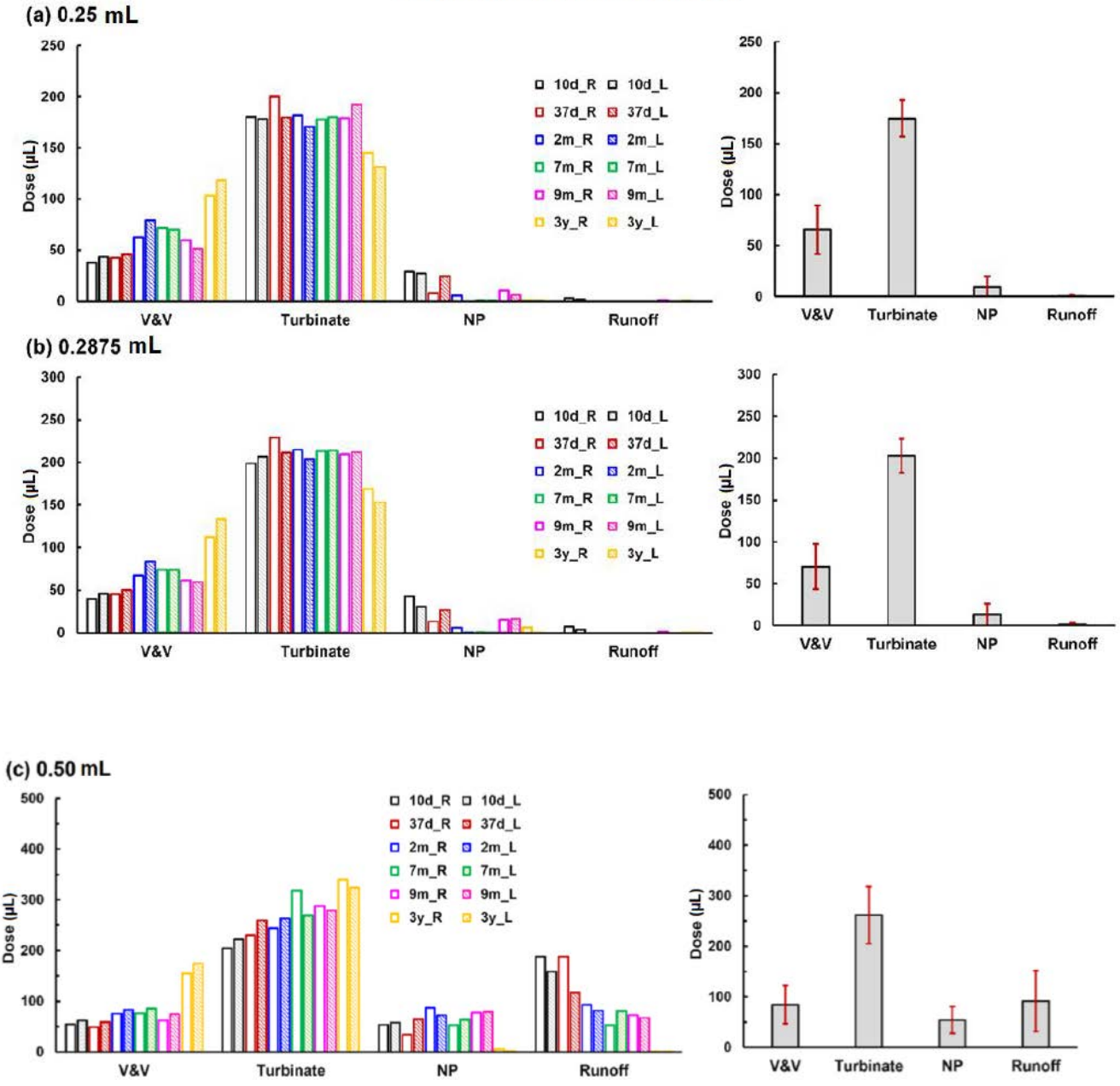
As in the original report; and

3) 7-month-old female model
4) 37-day-old male model
5) 2-month-old male model
6) 9-month-old female model

Each of the models was based on the CT images of a distinct individual. Although the number is still low due to scarcity of data in the literature, these six models represent a more diverse range of ages and subjects than the original report. The modeling results demonstrated inter-subject and intra-subject (between left and right nasal passages) variabilities in the deposition of the dose across different nasal anatomical regions, with the pharynx and beyond region (run-off) consistently (across all ages) receiving minimal fraction of the dose when the volume of spray is (b) (4) or (b) (4) µL. This addressed DARS's original concern about variability and modeling uncertainty.

Comparison of Regional Dose Distribution and Run-Off Volume among the Six Different Models

(V&V: valve and vestibule; NP: nasopharynx; Beyond: pharynx and beyond, or run-off; R: right passage; L: Left passage)



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Are the model predictions consistent with any external, independent experimental data?

The credibility of model evaluations can be assessed by comparing model predictions to independent experimental results. Hosseini et al. [1] constructed in vitro multi-sectional airway models and studied the distribution of nasal sprays in adults and children. They found that a spray volume of 0.5 mL (into each nostril) resulted in ~30% run-off (into the throat) for their 2-year-old and 5-year-old in vitro model. In contrast, the sponsor's 3-year-old (the closest age to the ages used by Hosseini et al.) computational model predicted 0.1% run-off. Such a 30% difference might represent the highest possible degree of prediction uncertainty from the sponsor's model. It is highly likely that the different device- and product-related parameters (droplet size distribution, spray plume angle, droplet release velocity, liquid density and viscosity) led to such significant differences. If the sponsor can use their model and Hosseini et al. parameters to reproduce the run-off fraction from a nasal spray of 0.5 mL as measured by the in vitro model, then the prediction uncertainty from the sponsor model could be significantly reduced, and the credibility of the sponsor's modeling results for (b) (4) µL (the intended volume of their product) could be significantly increased.

Is the proposed spray volume 0.25 mL consistent with clinical practice and recommendation for pediatric nasal administration?

The intended spray volume of (b) (4) µL (0.25 mL) is within the range of recommended volume for pediatric nasal administration (0.2 – 0.3 mL) [2]. Since children younger than 1 year old may have the most fraction of run-off due to their small nasal airway surface area, we conducted a literature review to examine the spray volume used for nasal administration to infants. The results (table below) suggests that in clinical practice, nasal administration to infants usually uses a volume less than 0.3 mL, which covers the intended spray volume of the sponsor's product (0.25 mL). Of note, these studies were not designed to assess whether run-off occurred and the potential consequences.

Active drug	Volume	Age of patients	Administration method	Reference
fentanyl	0.3 mL	Neonates	mucosal atomization device	3
nalbuphine	0.02 – 0.1 mL	1-3 months	mucosal atomization device	4
fentanyl	0.1 – 0.3 mL	Neonates (palliative care)	Syringe	5

Summary and Conclusions

In this new modeling and simulation report, the sponsor expanded the series of nose-throat geometry models to cover more pediatrics across additional ages. Now this series is based on six pediatrics' CT scan images, five of them younger than 1 year old. The results demonstrated age-dependent inter- and intra-subject variability. This addressed DARS' original concern of the model(s) not capturing variability in pediatric nasal anatomy.

The modeling results suggested that the intended dose of 0.25 mL would result in very little run-off in a 10-day-old model. The proposed volume of 0.25 mL is within the recommended range for pediatric nasal

administration and is consistent with clinical practice of delivering drugs to infants through nasal route. However, the sponsor's model also predicted a spray volume of 0.5 mL would result in very little run-off in a 3-year-old model. There is literature data that suggest 0.5 mL nasal spray resulted in substantial (~30%) run-off in 2-year-old and 5-year-old in vitro models. Using the sponsor's model to explain such an apparent discrepancy could significantly decrease the prediction uncertainty of the sponsor model and increase the credibility of its prediction of minimal run-off with a spray of 0.25 mL.

Recommendation to Sponsor

The credibility of a computational model can be evaluated by comparing the modeling results to external, independent experimental results. For example, your model predicted very little (~0.1%) run-off in the 3-year-old model when the spray volume is 0.5 mL. Hosseini et al. [1] constructed a 3D print-based in vitro model for 2 and 5 years old and measured a run-off fraction of ~30% when the spray volume is 0.5 mL (into each nostril). It is understandable that differences in study conditions (head position, droplet size, droplet release velocity, number of doses etc.) may underlie the apparent difference. Please provide your assessment for the differences between your simulations and this publication. One approach would be to use the Hosseini et al. study conditions in your model and simulate run-off. If your model can reproduce the measured run-off fraction (~30%) in your 3-year-old model, which is close to 2 and 5 years old used by Hosseini, or if your model predicts a different value but there is a valid explanation, then the credibility of your model would be significantly increased.

References and Supporting Documents

1) Hosseini et al. In vitro measurement of regional nasal drug delivery with flonase, flonase sensimist, and mad nasal in anatomically correct nasal airway replicas of pediatric and adult human subjects. Journal of Aerosol Medicine and Pulmonary Drug Delivery. (2019) 32:374
2) Wolfe et al. Intranasal medication delivery for children: a brief review and update. Pediatrics. (2010) 126:532
3) Sindhur et al. Intranasal fentanyl for pain management during screening for retinopathy of prematurity in preterm infants: a randomized controlled trial. Journal of Perinatology (2020) 40:881
4) Pfiffner et al. Pharmacokinetics and tolerability of intranasal or intravenous administration of nalbuphine in infants. Archives of Disease in Childhood (2023) 108:56
5) Harlos et al. Intranasal fentanyl in the palliative care of newborns and infants. Journal of Pain and Symptom Management (2013) 46:265

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/s/

TRACEY B LEE
01/25/2023 07:16:01 AM

REBECCA L HERNANDORENA
01/25/2023 07:38:21 AM

JEFFRY FLORIAN
01/25/2023 07:57:15 AM

M E M O R A N D U M

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

DATE: 11/14/2022

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 208969

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in June 2022, which falls within the surveillance interval. The inspection was conducted under the following submission: (b) (4)

OSIS concluded that data from the reviewed studies were reliable.

OSIS conducted a Remote Regulatory Assessment (RRA) for the site in July 2022, which falls within the surveillance interval. The RRA was conducted under the following submission: (b) (4)

OSIS concluded that data from the reviewed studies were reliable.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	West Coast Clinical Trials (WCCT) Global, Inc.	5630 Cerritos Avenue, Cypress, CA
Analytical	Amphastar Pharmaceuticals, Inc.	Research and Development Department, 11570 6th Street, Rancho Cucamonga, CA

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/s/

JOSHUA L PEREZ
11/25/2022 03:00:15 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 22, 2018

To: Shelly Kapoor, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 208969
OPDP labeling comments for Naloxone Nasal Spray
Labeling Review

OPDP acknowledges receipt of your June 3, 2016, consult request for the proposed Package Insert for Naloxone Nasal Spray. Reference is made to the February 17, 2017, Compete Response (CR) letter. As a result, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DAAAP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
01/22/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	February 21, 2017
To:	Sharon Hertz, MD Director **Division of Anesthesia, Analgesia and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	(b) (4) (naloxone hydrochloride) Nasal Spray
Dosage Form and Route:	Intranasal
Application Type/Number:	NDA 208969
Applicant:	Amphastar Pharmaceuticals, Inc.

1 INTRODUCTION

On April 18, 2016, Amphastar Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) 208969 for (b) (4) (naloxone hydrochloride) Nasal Spray. The proposed indications for (b) (4) (naloxone hydrochloride) are

(b) (4)

On June 3, 2016, the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for (b) (4) (naloxone hydrochloride) Nasal Spray.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for (b) (4) (naloxone hydrochloride) Nasal Spray.

2 CONCLUSIONS

Due to outstanding deficiencies, DAAAP issued a Complete Response (CR) letter on February 17, 2017. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

MORGAN A WALKER
02/21/2017

BARBARA A FULLER
02/21/2017

LASHAWN M GRIFFITHS
02/21/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Physical Medicine, Orthopedic, Neurology, and Dental Devices Branch

Date: February 16, 2017

To: Julia Pinto
CDER/DAAAP
W.O. 21-2675
julia.pinto@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Steven Kinsley
steven.kinsley@fda.hhs.gov

Through: Vesa Vuniqi, Acting Branch Chief, POND/DMQ/OC/CDRH

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From: Katelyn R. Bittleman, CSO, POND/DMQ/OC/CDRH

Applicant: Amphastar Pharmaceuticals, Inc.
11570 6th Street
Rancho Cucamonga, California 91730
FEI#: 3002936358

Application # NDA 208969

Consult # ICC1600285

Product Name: Naloxone HCl Nasal Spray

Pre-Approval Inspection: No

Documentation Review: No Additional Information Required

Inspection Review: Additional Information Required

Final Recommendation: **DELAY**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 208969.

PRODUCT DESCRIPTION

Intranasal Naloxone Hydrochloride (HCl), the subject of this NDA, consists of (i) a sterile Naloxone HCl solution (b) (4) . The applicant states the indications for use as " (b) (4) "

(b) (4)

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Amphastar Pharmaceuticals, Inc.
   11570 6th Street
   Rancho Cucamonga, California 91730-6025
   FEI: 3002936358

Responsibility – This firm is the applicant. They are responsible for the combination product as a whole and are subject to applicable 21 CFR 820 regulations.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has not been inspected.

Inspection Recommendation:
An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part;
- NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the ***next*** inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

2. International Medication Systems, Ltd.
   1886 Santa Anita Ave.
   South El Monte, CA 91733
   FEI: 2016148

Responsibility – Manufacturing, packaging, labeling and control operations, distribution, as well as release and stability testing of drug product (aka device constituent).

Inspectional History –

a. An analysis of the firm's inspection history over the past 2 years showed that inspections were conducted on 1/30/2017-2/9/2017 and 11/29/2016-12/20/2016.
b. The 2016 inspection covered drug GMP and medical device QS requirements. The drug GMP processes inspected was classified VAI, while the medical device QS processes inspected was classified NAI. The medical device QS inspected products covered, included prefilled syringes for allergens and vaccines.
c. The 2017 inspection covering drug GMP and medical device QS requirements was completed on 2/9/2017. An 8-item 483 was issued to the firm with five of the observations being related to device QS. The EIR and a number of the collected evidence are currently unavailable for review. An expedited review was requested based on the information available.

Inspection Recommendation:
An inspection is not required because:

- A device QS inspection was recently completed. However, the EIR and evidence must be evaluated.

3. [redacted] (b) (4)

Responsibility – [redacted] (b) (4)

Inspectional History –

a. An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on [redacted] (b) (4) The inspection covered drug GMP requirements and was classified VAI.
b. An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on [redacted] (b) (4) The inspection covered medical device QS requirements and was classified NAI. The device identified during the inspection was [redacted] (b) (4)

Inspection Recommendation:
An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. IMS is identified as the firm which manufacturers the device constituent. This firm states they comply with 21 CFR 210 and 21 CFR 211 regulations but does not specifically mention the applicable 21 CFR 820 (820.20, 820.30, 820.50, and 820.100) callouts noted in the combination products section 21 CFR 4.

The device constituent is identified as a nasal spray applicator which falls under the regulation 21 CFR 874.5220. When classified as a device alone, these devices are classified as low risk (Class I devices). While this device constituent is used in conjunction with a drug constituent, the nature of the combination product does not significantly affect the design and manufacturing of the device constituent or the safety and effectiveness of the device constituent. The intended use of the drug is to counteract opioid overdose in an emergency situation. The combination product is intended to be used by layperson who may or may not have prior experience with the combination product or medical emergency situations. The intended use of this combination product increases the risk profile of the device constituent. The design and manufacturing of the design constituent and the combination product as a whole is critical for safe and effective use. Failure of the device constituent can lead to ineffective delivery of a life-saving drug which can cause serious adverse events and death.

21 CFR 874.5220 is stated as follows:
"§874.5220 Ear, nose, and throat drug administration device.

(a) *Identification*. An ear, nose, and throat drug administration device is one of a group of ear, nose, and throat devices intended specifically to administer medicinal substances to treat ear, nose, and throat disorders. These instruments include the powder blower, dropper, ear wick, manual nebulizer pump, and nasal inhaler.

(b) *Classification*. Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in §874.9. If the device is not labeled or otherwise represented as sterile, it is exempt from the current good manufacturing practice requirements of the quality system regulation in part 820 of this chapter, with the exception of §820.180, with respect to general requirements concerning records, and §820.198, with respect to complaint files."

Management Control, 21 CFR 820.20

The following information request was sent to the applicant on January 25th, 2017:

> "You state that the nasal spray device is manufactured by International Medication Systems, Ltd.in South El Monte, California. Please provide a summary of the current management structure which outlines who has the executive responsibility to manage, perform, and assess work affecting quality of the product and related controls to ensure that the quality policies are appropriately implemented and followed, and the product is appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements, as per 21 CFR 820.20."

Review of Firm Response Sent 2/1/2017: IMS is a wholly owned subsidiary of Amphastar Pharmaceuticals, Inc. IMS has developed its quality management system to satisfy the requirements outlined in 21 CFR 210 and 211 for pharmaceuticals and the applicable sections of 21 CFR 820 for combination products.

(b) (4)

[redacted]

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

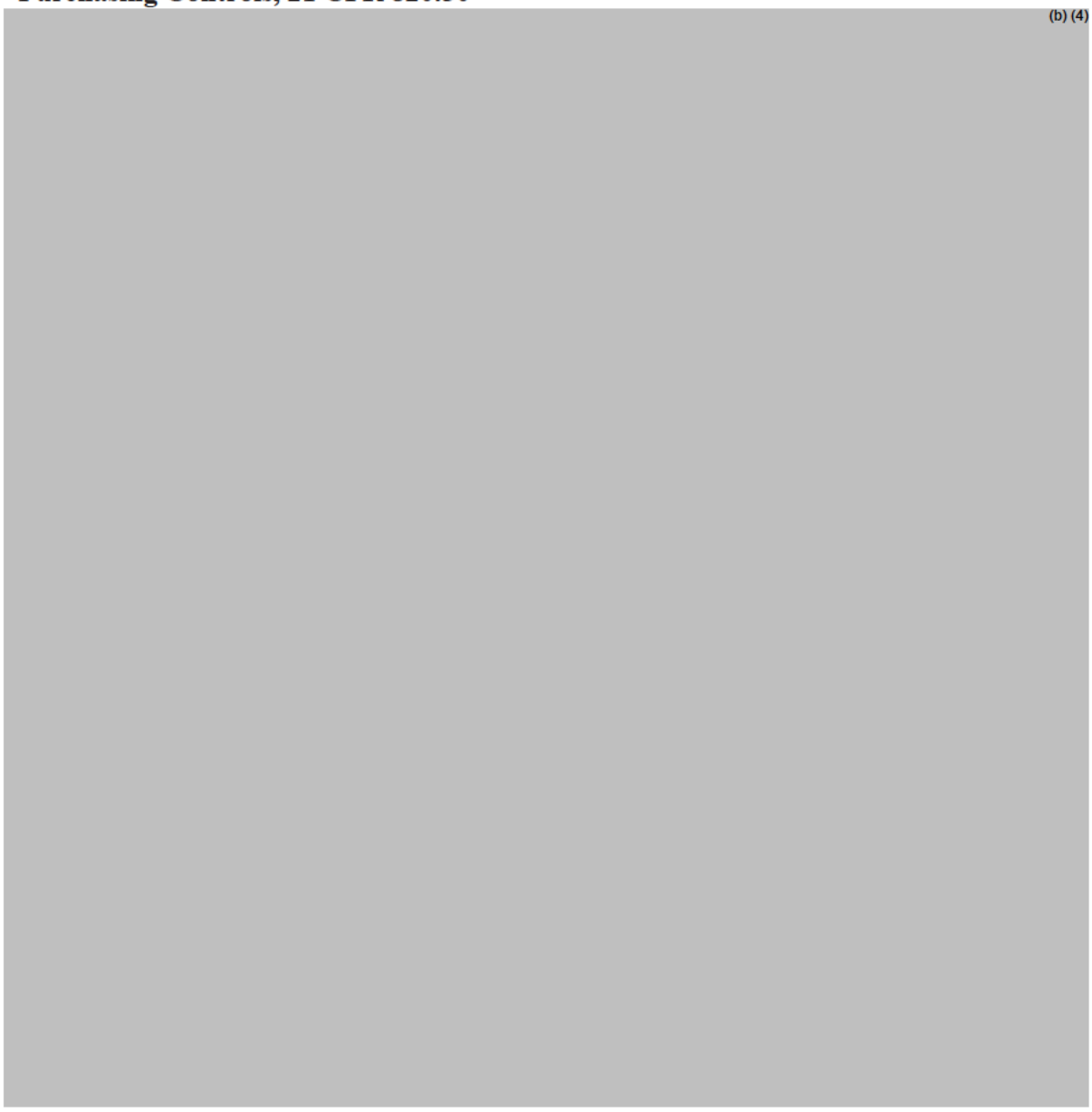
Design Control, General, 21 CFR 820.30

During the inspection of the IMS facility on 11/29/2016, it was noted that the combination product under review is listed by the firm as subject to design control requirements (EIR page 18-19).

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

(b) (4)



(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm did not provide detailed information or a summary on the CAPA system as it relates to the device constituent in their submission. The inspection of the IMS facility (11/2016) reviewed a number of CAPA documents for multiple products. No reviewed CAPAs were related to the subject product of this NDA. It was unclear if IMS is responsible for CAPA or that responsibility lies with the applicant, Amphastar Pharmaceuticals.

The following information request was sent to the applicant on January 25th, 2017:

> "It is unclear how corrective and preventative actions (CAPA) procedures are implemented in regards to the nasal spray applicator device. Please provide a summary of your process for Corrective and Preventive Actions (CAPA). The CAPA process is used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100."

Review of Firm Response Sent 2/1/2017: The firm provided a summary of SOPs regarding non-conforming product and CAPA procedures. (b) (4)

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

(b) (4)

[redacted]

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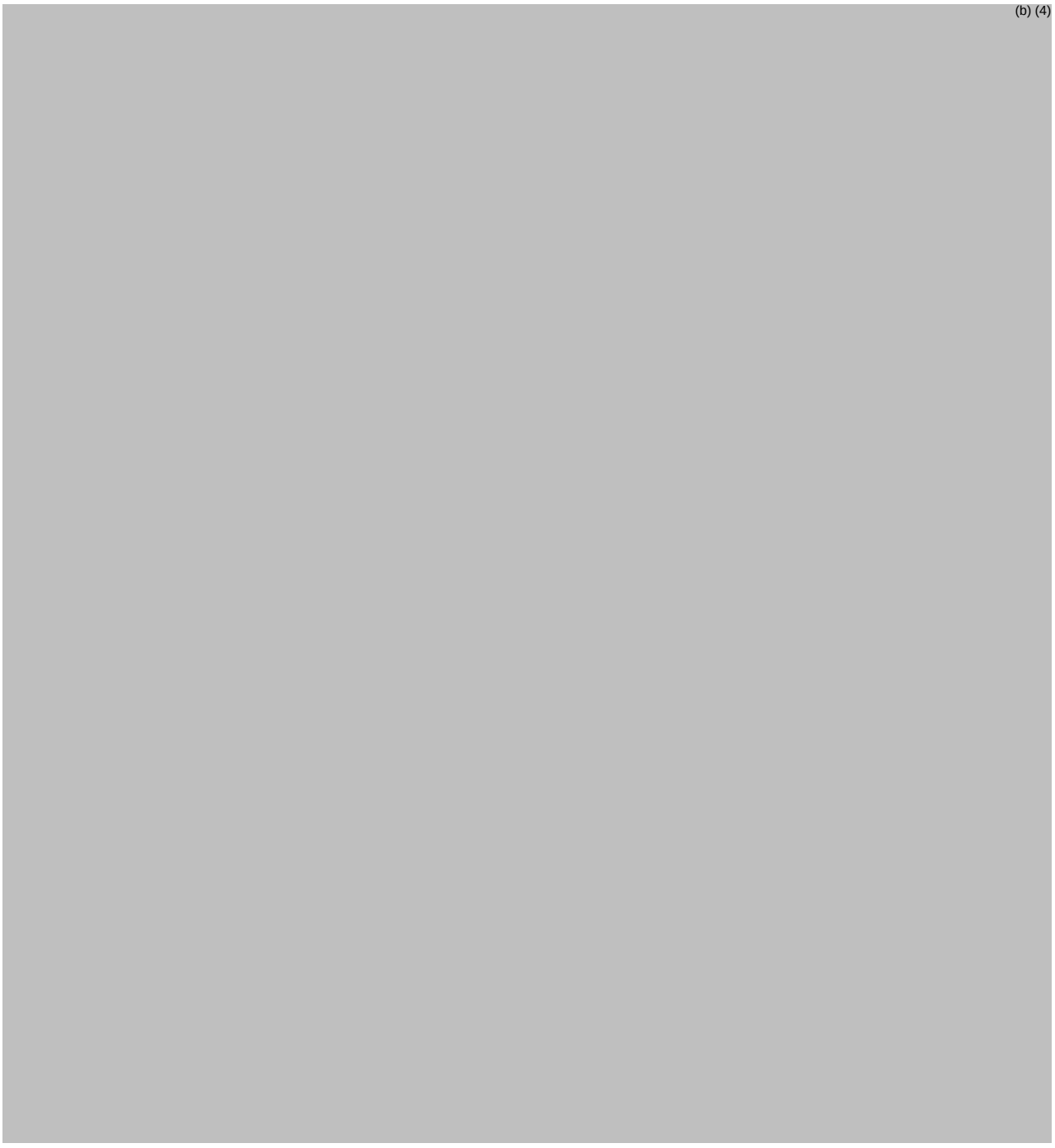

RECOMMENDATION

The application was searched for documents pertaining to the manufacturing of the combination product. Additional information was provided before the inspection at International Medication Systems, Ltd. was conducted.

A preliminary review of the most recent inspection (1/30/2017-2/09/2017) at the IMS facility was completed. While the EIR and some evidence were not available, the

available documents including the FDA 483, some collected evidence, and the firm's response dated February 14, 2017 were reviewed for compliance with the applicable Quality System Requirements. The district has recommended a classification of OAI. CDRH cannot determine the supportability of this classification until all evidence has been provided for review.

Due to the risk to patients associated with device failure and the severity of the observations, it is recommended that the application be delayed until the inspection of the IMS facility is reviewed and finalized. CDRH/OC/DMQ requests to review the EIR and be assured all violations (if applicable) are rectified prior to final recommendation of this NDA.

Katelyn Bittleman -S
2017.02.17 17:03:17 -05'00'

Katelyn R. Bittleman

Prepared: KRBittleman: 2/15/2017
Reviewed: VVuniqi: 2/17/2017

CTS No.: ICC1600285
NDA 208969

To: ORA

INSPECTIONAL GUIDANCE

Firm to be inspected:

1. Amphastar Pharmaceuticals, Inc.
   11570 6th Street
   Rancho Cucamonga, California 91730-6025
   FEI: 3002936358

CDRH recommends that the next routine inspection of the firm listed above covers compliance with all the requirements of 21 CFR part 4, including the applicable Quality System (21CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100).

REGULATORY STRATEGY

If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related. If the inspection is classified as OAI with violations related to the device, the establishment inspection report (EIR) for the firm should be shared with CDRH (the EIR should be assigned to CDER and then sent to CDRH as a consult for review).

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Katelyn R. Bittleman
Consumer Safety Officer
Physical Medicine, Orthopedics, Neurology, and Dental Devices Branch
Division of Manufacturing and Quality
Office of Compliance, WO66 RM 3451
Phone: 240-402-1478

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Vesa Vuniqi
Acting Branch Chief
Physical Medicine, Orthopedics, Neurology, and Dental Devices Branch
Division of Manufacturing and Quality
Office of Compliance, WO66 RM 3452
Phone: 301-796-5773

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/s/

STEVEN A KINSLEY
02/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Intercenter Consult Memorandum

Device Constituent Part Design Review: CDER NDA 208969 - CDRH ICC1600304

Date: January 5, 2017

To: Shelly Kappor, OMPT/CDER/OND/ODEII/DAAAP

From: Robert Meyer, Mechanical Engineering Reviewer
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Subject: Device Constituent Part Design Review: ICC1600304/ NDA 208969

Drug: Naloxone HCL

Device: Nasal spray (b) (4)

Sponsor: Amphastar Pharmaceuticals, Inc.

Recommendation: Complete Response – deficiencies included in Section X

Note: Italicized text in this review is copied from provided Sponsor Documentation, unless noted.

I. Purpose

This consult is a review of the documents provided by the Sponsor regarding the justification they provided to demonstrate the subject nasal spray device adequately and reliably functions as intended.

(b) (4)

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(b) (4)

X. **Recommendation – Complete Response**

Based on the available data, we are unable to conclude that the device performance and reliability is adequate to achieve a reasonable benefit/risk balance for the intended use of the combination product. We recommend a complete response letter include the following deficiencies:

1. (b) (4) Please modify the delivery accuracy verification method (b) (4) are not captured in the analysis and repeat the testing to be consistent with the specified device performance specifications.

2. The Agency acknowledges that your currently proposed reliability specification at expiry is (b) (4)). Given that the product is intended for emergency treatment of opioid overdose, the Agency believes that this reliability specification is not acceptable. We request that you the lowest failure rate achievable that can be controlled for through design and manufacturing controls. (b) (4)

(b) (4)

(b) (4)

XI. Concurrence Table

Digital Signature Concurrence Table	
Reviewer Sign-Off	Robert Meyer -S 2017.01.05 08:55:51 -05'00'
Branch Sign-Off	Alan M. Stevens -S Alan M. Stevens -S 2017.01.05 09:07:57 -05'00'

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/s/

SONAM S KAPOOR
02/15/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Mona Khurana, M.D., Acting Pediatric Team Leader
Division of Pediatric and Maternal Health
Office of Drug Evaluation IV

Through: John J. Alexander, M.D., M.P.H.
Deputy Director

To: Division of Anesthesia, Analgesia, and Addiction Products

Drug Name: (b) (4)

Active Ingredient: Naloxone Hydrochloride Dihydrate

Therapeutic Class: Opioid Antagonist

Subject: Review of Pediatric Assessment

Applicant: Amphastar Pharmaceuticals, Inc.

Materials Reviewed

- Contents of NDA submission in DARRTS
  - Module 1.9.6 Agreed Initial Pediatric Study Plan
  - Module 2.3 Quality Overall Summary
  - Module 2.5 Clinical Overview
  - Module 3 Drug Product
- Relevant Documents under IND 124672
  - March 12, 2015 Meeting Minutes for Type B Pre-IND Meeting held on February 10, 2015 (DARRTS Reference ID 3714808)
  - November 27, 2015 Meeting Minutes from Type B Pre-NDA Meeting held November 5, 2015 (DARRTS Reference ID 3852741)
- December 2015 DPMH Memorandum under NDA 208411

Consult Request

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) to evaluate the adequacy of the applicant's pediatric assessment in supporting approval of the proposed intranasal (IN) naloxone hydrochloride (HCl) drug product in the full pediatric age range. DAAAP is also requesting DPMH provide pediatric labeling recommendations.

I. Background

A. Proposed Drug Product

The proposed drug product, (b) (4) is designed as a single-use IN spray device consisting of a pre-filled syringe containing (b) (4) milliliters (mL) of a sterile (b) (4) milligram (mg)/mL solution of naloxone HCl dihydrate. (b) (4) The applicant is proposing a fixed (b) (4) IN dose in adults and pediatric patients of all ages that would be delivered in a (b) (4) mL volume. The applicant is proposing to co-package two dosing units in each kit.

(b) (4) is being developed for immediate use as emergency therapy for the complete or partial reversal of opioid depression, including respiratory depression, in both outpatient and community settings where opioids may be present. The applicant states the primary purpose for (b) (4) is to provide a user-friendly, needle-free route of administration for medical professionals, first responders, and at home family members.

B. Regulatory History of New Drug Application (NDA) 208969

(b) (4) was developed under investigational new drug (IND) 124672. FDA granted the applicant Fast Track designation in March 2015[1] and Rolling Review in January 2016.[2]

FDA received NDA 208969 on April 19, 2016. This NDA was submitted under the 505(b)(2) pathway and relies on FDA's previous findings of efficacy and safety for Narcan for injection (NDA 016636) as the listed drug. The NDA is supported by two comparative bioavailability studies conducted to demonstrate that (b) (4) achieves comparable or higher systemic exposure and comparable or quicker onset of action compared to an approved dose and route of administration for naloxone HCl (e.g. intramuscular injection of 0.4 mg naloxone). DAAAP previously conveyed to the applicant that use of a generic naloxone HCl comparator would be

[1] March 27, 2015 Grant Fast Track Letter in DARRTS under NDA 208969 (DARRTS Reference ID 3722574)

[2] January 12, 2016 Grant Rolling Review Letter in DARRTS under NDA 208969 (DARRTS Reference ID 3872455)

acceptable since Narcan is no longer marketed.[3] The Prescription Drug User Fee Act goal date is February 19, 2017.

The following is a summary of key discussion points at milestone meetings held under IND 124672 in which clinical and regulatory issues relevant to the pediatric population were raised:

Type B Pre-IND Meeting:[3]

- DAAAP conveyed concerns (b) (4)
- (b) (4) Therefore, DAAAP strongly suggested the applicant develop (b) (4)
- (b) (4) DAAAP recommended the applicant consider this information during their formulation development.
- DAAAP informed the applicant their proposed new IN route of administration for naloxone would trigger the requirement for a pediatric assessment under the Pediatric Research Equity Act (PREA). DAAAP suggested the applicant consider addressing PREA requirements by providing a justification (e.g. from the literature, approved Narcan labeling) for why their product, which contains a fixed dose of naloxone, is acceptable for all pediatric age ranges to support pediatric labeling for their product. As part of the justification, DAAAP stated the applicant must provide data for why the volume per dose is appropriate for the nasal cavities of the entire pediatric age range. DAAAP stated they did not expect the pediatric nasal mucosa to be sufficiently different from adults and to adversely impact the systemic absorption of naloxone, but the total amount of fluid that may be instilled into a smaller nasal cavity is anticipated to be less.

[3] March 12, 2015 Meeting Minutes for Type B Pre-IND Meeting held on February 10, 2015 (DARRTS Reference ID 3714808)

DAAAP stated the applicant should develop a formulation of IN naloxone for use in all patients (adults and pediatric) that takes into consideration the smaller volume of the pediatric nasal cavity.

- DAAAP advised the applicant to conduct a comprehensive use-related risk analysis to identify the risks associated with (b) (4) the proposed product.
- In the absence of conducting non-clinical IN toxicity studies, DAAAP informed the applicant they must evaluate local IN tolerability and safety in their human pharmacokinetic (PK) studies through examination of the nasal and oropharyngeal mucosa.

Type B Pre-NDA Meeting:[4]

- DAAAP expressed concern that the applicant's new proposed (b) (4) is unlikely to be appropriate for the entire pediatric age range and that, if the applicant cannot provide support for the product in all pediatric age ranges with regards to dose, volume, and device, then they will need to develop an age-appropriate formulation and consider using that formulation for the entire pediatric age range to avoid having different products for different age groups.
- DAAAP agreed with co-packaging of two dosing units in each kit to ensure a second dose will be available when required in cases of an inadequate response, a device malfunction, or an administration error.
- DAAAP agreed that data from a human factors validation study are required to support safety and effectiveness of the proposed product for the intended uses and environments and that the acceptability of the data will be a review issue.

FDA issued an Agreed initial Pediatric Study Plan (iPSP) to the applicant on October 13, 2015, and this Agreed iPSP was included in the current NDA submission. In the Agreed iPSP, the applicant states they have no plan for extrapolation of adult efficacy data to the pediatric population since the safety and effectiveness of naloxone HCl in all pediatric populations have been established as described in the approved labeling for the listed drug (Narcan). The Agreed iPSP contains no requests for age-specific waivers or deferrals of required pediatric studies.

II. DPMH Review of Pediatric Assessment

[4] November 27, 2015 Meeting Minutes from Type B Pre-NDA Meeting held November 5, 2015 (DARRTS Reference ID 3852741)

The NDA included data from two bioavailability studies [redacted]

The pediatric assessment consists of the applicant's review of the published literature and published practice guidelines to justify use of a fixed [redacted] dose of [redacted] in all pediatric ages. The applicant also leveraged pediatric use information from the approved labeling of the listed drug to support the safety and efficacy of [redacted] in all pediatric ages.

Although [redacted] met DAAAP's PK standard for approval of novel naloxone drug products, failures by untrained laypersons to use the product correctly in the Human Factors Validation Study raised concerns by the review team that failure to deliver the effective dose [redacted] would lead to an unfavorable risk benefit profile not only in adults but also in pediatric patients requiring an effective naloxone dose as life-saving treatment in an emergency setting. [redacted]

Additionally, [redacted] has the potential to lead to run-off into the posterior pharynx with the possibility of entry into the lungs and consequent aspiration and other respiratory complications, especially in the youngest pediatric patients.[5] FDA has encountered this safety issue with other IN drug products in development when IN delivery has been studied in younger pediatric patients [redacted]

[5] Grassin-Delyle, Buenestado A, Naline E, et al. Intranasal Drug Delivery: An Efficient and Non-Invasive Route for Systemic Administration. Focus on Opioids. Pharmacology & Therapeutics 134: 366-379, 2012.

[6] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022382s000ltr.pdf; accessed at Drugs@FDA 11/1/15

(b) (4)

FDA has approved multiple IN drug products for pediatric use, but none are approved for use down to birth and only one is approved for use within the first year of life (see Table 1). Importantly, the approved IN drug products administer volumes per actuation ranging from 0.075 to 0.1 mL (b) (4)

Table 1. FDA Approved IN Drug Products for use in Pediatric Patients

Drug	Nasal Formulation	Pediatric Indication	Pediatric Age Range
Prescription			
Minirin (desmopressin acetate) N021333	Metered Spray: 100 µL/actuation	Antidiuretic therapy in central diabetes insipidus	3 months to 12 years
Nasonex (mometasone furoate monohydrate) N020762	Metered spray: 100 µL/actuation	Nasal symptoms of allergic rhinitis, nasal congestion associated with seasonal allergic rhinitis, prophylaxis of seasonal allergic rhinitis	2 years and older
Qnasl (beclomethasone) N202813	Aerosol spray: Volume/actuation unspecified	Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis	4 years and older
Atrovent (ipratropium	Metered spray: 70 µL/actuation	Symptomatic relief of rhinorrhea associated with	6 years and older

(b) (4)

Drug	Nasal Formulation	Pediatric Indication	Pediatric Age Range
bromide) N020393		allergic and non-allergic perennial rhinitis	
Rhinocort (budesonide) N020746	Metered spray: Volume/actuation unspecified	Temporary relief of hay fever or other upper respiratory allergies	6 years and older
Beconase AQ (beclomethasone dipropioante monohydrate) N019389	Metered spray: Volume/actuation unspecified	Relief of seasonal or perennial allergic and nonallergic rhinitis	6 years and older
Patanase (olapatadine HCl) N021861	Metered spray: 100 µL/actuation	Relief of symptoms of seasonal allergic rhinitis	6 years and older
Over-the-Counter			
Nasacort Allergy 24 Hour (triamcinolone acetonide) N020468	Metered spray: Volume/actuation unspecified	Temporary relief of hay fever or other upper respiratory allergies	2 years and older

(Source: created by this reviewer from product labelings retrieved from FDALabel); µL: microliters

The applicant cited multiple references to support the safe and effective use (b) (4) but the referenced publications were either general reviews of IN drug delivery[11,12] or were published studies supporting the successful use of other IN drugs for seizure control, acute pain control, and pre- and intra-procedure sedation; none of these drugs are currently FDA approved for IN use in pediatric patients for the described indications.[13,14,15,16]

III. Conclusions

Failures by untrained laypersons to use (b) (4) correctly in the Human Factors Validation Study raise concerns that (b) (4) may result in treatment failure in pediatric patients due to inadequate delivery of the full intended IN dose. Additionally, (b) (4)

[11] Warrington SE and Kuhn RJ. Use if Intranasal Medications in Pediatric Patients. Orthopedics. 34(6): 456, 2011.

[12] Wolfe TR and Braude DA. Intranasal Medication Delivery for Children: A Brief Review and Update. Pediatrics 126(3): 532-537, 2010.

[13] Humphries LK and Eiland LS. Treatment of Acute Seizures: Is Intranasal Midazolam a Viable Option? The Journal of Pediatric Pharmacology and Therapeutics 18(2): 79-87, 2013.

[14] Goldman RD. Intranasal Drug Delivery for Children with Acute Illness. Current Drug Therapy 1:127-130, 2006.

[15] Chokshi AA and Patel VR. Evaluation of Intranasal Midazolam Spray as a Sedative in Pediatric Patients for Radiological Imaging Devices. Anesthesia Essays Research 7(2): 189-193, 2013.

[16] Cole J, Shepherd M, Young P. Intranasal Fentanyl in 103 Year Olds: A Prospective Study of the Effectiveness of Intranasal Fentanyl as Acute Analgesia. Emergency Medicine Australasia 21(5): 395-400, 2009.

(b) (4) has the potential to lead to run-off into the posterior pharynx with the possibility of entry into the lungs and consequent aspiration and other respiratory complications, especially in the youngest pediatric patients. The pediatric assessment does not adequately address the potential safety concerns associated (b) (4) to support use down to birth.

IV. Recommendations

DPMH recommends against approval of (b) (4) for the proposed indication in the pediatric population. Since pediatric studies to assess the safety of the proposed (b) (4) for the proposed indication are challenging to conduct from both an ethical and feasibility perspective, the applicant should consider re-formulating their product to provide a single formulation, which delivers an IN volume per actuation consistent with that of currently approved IN drug products to ensure the product can be safely used in adults and pediatric patients down to birth.

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/s/

MONA K KHURANA
01/18/2017

JOHN J ALEXANDER
01/19/2017

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 17, 2017
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208969
Product Name and Strength:	(b) (4) (Naloxone) Nasal Spray (b) (4)
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amphastar Pharmaceuticals
Submission Date:	April 18, 2016
OSE RCM #:	2016-963 and 2016-964
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

Amphastar Pharmaceuticals, Inc. submitted their human factors (HF) validation study results, and labels and labeling for (b) (4) (naloxone hydrochloride) nasal spray, (b) (4), proposed for the emergency treatment of opioid overdose. (b) (4) nasal spray will be supplied in a box containing two single dose nasal spray devices, each one in a separate blister. (b) (4) . The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the HF validation study results, container labels, carton labeling, Quick Guide (QG) and prescribing information.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B N/A
Human Factors Study	C
ISMP Newsletters	D N/A
FDA Adverse Event Reporting System (FAERS)*	E N/A
Information Request Response	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 BACKGROUND

DMEPA preliminarily reviewed summarized HF validation study results (Study #1 results) submitted in September 2015 as part of a meeting package for a PreNDA meeting. DMEPA identified task failures from the Study #1 results (b) (4) Based on our evaluation, these failures could have a negative impact on the product's efficacy. However, Amphastar Pharmaceuticals, Inc. did not provide adequate justification for why further risk mitigation strategies should not be employed. Based on the results, we provided comments to Amphastar Pharmaceuticals, Inc. in November 2015 for their HF development program[1]. In response to these comments, Amphastar Pharmaceuticals, Inc. subsequently completed and submitted results of a second HF

[1] Memorandum of Meeting Minutes submitted in DARRTS, November 27, 2015. Accessed on September 16, 2016.

validation study (Study #2), which are the subject of this review. Amphastar Pharmaceuticals, Inc. did not submit a protocol for us to review prior to conducting Study #2.

Amphastar Pharmaceuticals, Inc.'s risk analysis prior to conducting HF validation study #2 determined that most errors occurred when (b) (4) These changes were tested in HF validation study #2.

(b) (4)

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Human Factors (HF) Validation Study Assessment

(b) (4)

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/s/

JAMES H SCHLICK
01/13/2017

BRENDA V BORDERS-HEMPHILL
01/16/2017

QUYNHNHU T NGUYEN
01/17/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	December 14, 2016
Reviewer:	Chaitali Patel, PharmD, BCPS, Safety Evaluator Division of Pharmacovigilance II
Team Leader:	Sara Camilli, PharmD, BCPS, Team Leader Division of Pharmacovigilance II
Product Name:	Naloxone hydrochloride
Subject:	Life-threatening adverse events in neonates and infants
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2016-2673

1 INTRODUCTION

This document evaluates cases in FDA's Adverse Event Reporting System (FAERS) for life-threatening adverse events following naloxone administration in neonates and young infants. This review was requested by the Office of Pediatric Therapeutics (OPT) and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) in preparation for the October 5, 2016 naloxone Advisory Committee (AC) meeting.

On September 30, 2016, the Division of Pharmacovigilance (DPV) received a request from DAAAP to evaluate FAERS for reports of naloxone exposure in neonates and infants, aged 0 to 1 year, which precipitated severe acute opioid withdrawal. During our discussion OPT and DAAAP noted they were interested in acute life-threatening adverse events such as pulmonary edema, seizures, and cardiac arrest. The naloxone product labeling warns of precipitation of opioid withdrawal in neonates who have been exposed to opioid *in utero*, and the consult request noted that few episodes of severe acute withdrawal syndrome in neonates have been documented in the medical literature. An excerpt of the warning statement is below and the reference to neonates is highlighted in bold. For full details, refer to the full prescribing information.[1] Appendix A lists the initial FDA approval dates, strength, dosage form, and route of administration for the marketed naloxone products.

> **----------WARNINGS AND PRECAUTIONS----------**
>
> **5.3 Precipitation of Severe Opioid Withdrawal**
>
> The use of NARCAN Nasal Spray in patients who are opioid-dependent may precipitate opioid withdrawal characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. **In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes. Monitor the patient for the development of the signs and symptoms of opioid withdrawal.**
>
> Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, monitor patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is

similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. In these settings, consider use of an alternative, naloxone-containing product that can be titrated to effect and, where applicable, dosed according to weight *[see Use in Specific Populations (8.4)]*.

The October 5, 2016 joint AC meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Committee was charged to discuss naloxone products intended for use in the community. The committees were asked to discuss the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in the community setting. The committees were also asked to discuss the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available.

In anticipation of the AC discussion on the presence of multiple doses of naloxone on the market and use in the pediatric population, including neonates and infants, DAAAP and OPT requested DPV to review FAERS data for reports of severe acute opioid withdrawal in the pediatric population following naloxone exposure.

On October 5, 2016, the advisory committees discussed and voted on several issues, including, requiring different minimum standards [comparable or greater exposure compared to 0.4 mg of naloxone injection] to support the approval of [naloxone] products intended for use in adults and children. The majority of the committee members voted "No", indicating that there should not be different minimum standards used to support the approval of products intended for use in adults and in children. A slight majority of the committee members voted to increase the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection. They noted the safety profile of naloxone is excellent based on forty years of history of safe use in even the tiniest infants.[a]

2 METHODS AND MATERIALS

DPV searched the FAERS database and the medical literature with the strategies described in Tables 1 and 2, respectively, for case reports of life-threatening adverse events following naloxone administration in neonates and infants.

Table 1. FAERS Search Strategy*	
Date of Search	September 30, 2016
Time Period of Search	All reports received through September 30, 2016
Search Type	FBIS Quick Query

[a] Additional details of the discussions are available in the meeting transcript.[2]

Table 1. FAERS Search Strategy*	
Product Terms	Product Active Ingredient: naloxone, naloxone hydrochloride
MedDRA Search Terms (Version 19.0)	All adverse events
Additional Filters Applied	Age: 0 – 1.99
* See Appendix B for a description of the FAERS database.	

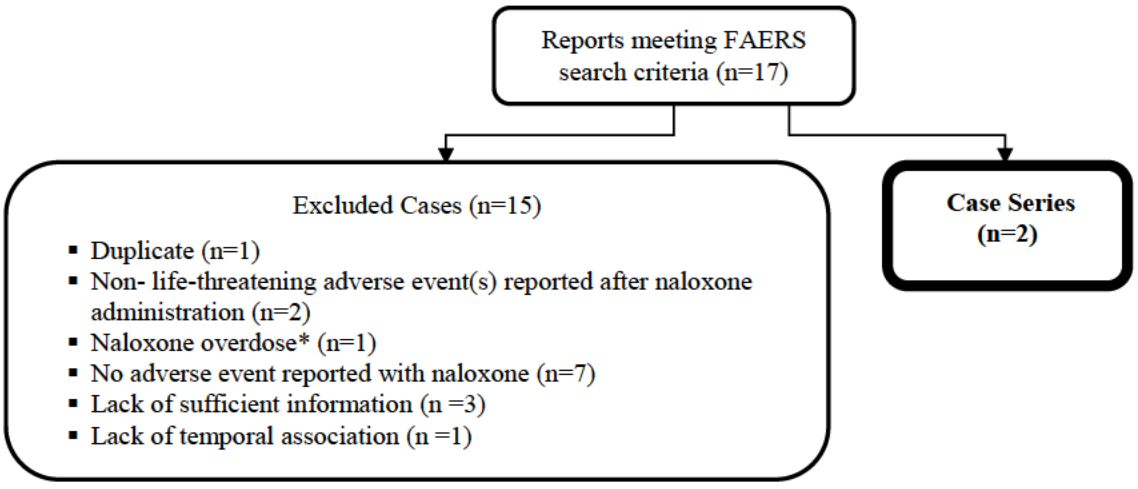
Table 2. Literature Search Strategy*	
Date of Search	December 3, 2016
Database	PubMed
Search Terms	naloxone AND (infant OR neonate)
Years Included in Search	All
Filters Applied	Article Type: case report

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 17 reports. After exclusions were applied, two cases were included in our case series of life-threatening adverse events following naloxone administration in neonates and infants. See Figure 1 below for the specific selection of cases.

Figure 1. FAERS Case Selection



* Summarized in Appendix C.

Life-threatening adverse events associated with naloxone exposure

FAERS case #6070713, United Kingdom, Received May 2006
A mother gave birth to a male (3.2 kg) at 39 weeks gestation. The mother received 50 mg pethidine (meperidine) during her 6 hours of labor. At 8 minutes after birth, the newborn received one dose of naloxone 200 (units not specified) IM in 0.5 mL for reversal of possible effects from maternal pethidine exposure. At 9 minutes after birth, the baby was "floppy and deteriorating rapidly" and had a cardiac arrest. The newborn was revived after 30 minutes. It was reported the events resolved on 9/24/2005. However, the newborn was transferred to the special baby care unit (SBCU) where he received ventilation and intravenous antibiotics for 5 days. He was discharged from the SBCU after 15 days.

Reviewer's comment: Based on the temporal association, a causal relationship between naloxone and the cardiac arrest cannot be excluded. Cardiac arrest, in the adult postoperative setting, has been described to occur due to abrupt opioid reversal. The method of delivery (e.g., vaginal or cesarean section) was not reported.

FAERS case #6907364, Australia, Received February 2009
A published case report[3] describes a 24-year-old mother who gave birth (27 weeks and 3 days gestation) via caesarean section to a preterm infant (485 g). There was no history of antenatal intravenous drug use. On day 7, the infant required an increase in ventilatory support and was administered inhaled nitric oxide and morphine (100 mcg/kg) for sedation. This 10-fold error in morphine dose dropped her mean arterial pressure from 31 to 20 mmHg within a 3 hour period. This led to the realization of the medication error. A bolus of naloxone 100 mcg/kg was subsequently administered via umbilical vein. Profound bradycardia and asystole immediately following administration of the bolus of naloxone. She responded to cardiopulmonary resuscitation and a dose of adrenaline (epinephrine) 0.1 mL/kg.

Reviewer's comment: Based on the temporal association, a causal relationship between naloxone and the adverse events of bradycardia and asystole cannot be excluded. However, rapid morphine reversal and residual morphine effects could have had a contributory role in the precipitation of these adverse events. In addition, the infant's preexisting condition at the time of the adverse event may have had a contributory role. Opioid overdose, necessitating reversal with naloxone, can inadvertently occur in a monitored setting or in the community. The life-threatening adverse events experienced by this neonate require immediate medical attention in any setting.

Appendix C summarizes an excluded naloxone case – naloxone overdose, which was of interest to OPT. The two cases comprising our case series and the excluded naloxone overdose case were previously provided to DAAAP and OPT via email on October 3, 2016. Appendix D lists the FAERS case numbers, FAERS version numbers, and manufacturer control numbers for all three cases.

3.2 LITERATURE SEARCH

DPV performed a literature search in the PubMed database. The search identified 95 case reports of naloxone exposure in infants. Of the 95 reports, 2 foreign cases described life-

threatening adverse events following naloxone administration. One case (FAERS #6907364; see Section 3.1) was reported in FAERS and the second is summarized below.

Gibbs[3] et al. describe a 25-year-old pregnant woman with a prior history of heroin abuse initiated methadone a year prior to conceiving. At the onset of labor she took methadone 60 mg. Eight hours later, a cesarean section was performed because of fetal distress. The term newborn was apneic and bradycardic (3.04 kg) requiring manual and then mechanical ventilation. By 4 minutes of age, naloxone 0.2 mg was administered intramuscularly for lack of spontaneous breathing. Two minutes after the naloxone administration, the newborn experienced a generalized convulsion refractory to diazepam (30 mg intravenously in divided doses), paraldehyde (1 mL rectally), and a loading dose of phenobarbitone (45 mg intravenously). Administration of an intravenous bolus of morphine (0.1 mg/kg) terminated the seizure, 30 minutes after it initiated. The morphine bolus was followed by a continuous infusion (0.1 mg/kg/hr) which was slowly tapered over the next week. After which, she became hyperactive, irritable, and restless, consistent with opioid withdrawal, but did not have any more convulsions. Serial ultrasound scans of her brain were all normal. The authors note they suspect the convulsions were due to acute opioid withdrawal because the convulsions precipitated by the naloxone administration responded to intravenous morphine.

4 REVIEWER'S COMMENTS

DPV identified three spontaneous cases describing life-threatening adverse events temporally associated with naloxone administration – two were retrieved from the FAERS database and one from the medical literature. All three are foreign cases.

Life-threatening adverse events have been reported following naloxone administration in various settings of use. One case describes reversal of an inadvertent morphine overdose in the neonate, one from intrapartum meperidine exposure, and one from antepartum methadone exposure. The adverse events were observed within 2 minutes of naloxone administration. The range of events described in the three cases includes cardiac arrest, profound bradycardia then asystole, seizures, hyperactivity, irritability, and restlessness. There were no deaths reported, potentially because of the availability of immediate medical attention in the inpatient setting.

The FAERS cases describe life-threatening adverse events (e.g., cardiac arrest and profound bradycardia leading to asystole) temporally associated with naloxone administration. However, the adverse event of profound bradycardia may be confounded by the opioid intoxication, known to cause cardiovascular depression. Opioid withdrawal generally causes tachycardia. The naloxone labeling states abrupt withdrawal of opioid depression, in the adult post-operative setting, may result in cardiac arrest.[1] The literature case report more closely represents clinical findings consistent with opioid withdrawal (e.g., seizures, hyperactivity, irritability, and restlessness).

There are limitations to FAERS data, including under-reporting. In particular, adverse events for naloxone are likely under reported due to the emergency setting of use.

The data reviewed does not change the known safety profile of naloxone in neonates and infants.

5 REFERENCES

1. Naloxone hydrochloride (naloxone), NDA 208411, 205787, 209862 – Approved Product Labels. Drugs@FDA Database. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208411lbl.pdf. Accessed 11/10/16.
2. U.S. Food and Drug Administration Advisory Committees. Summary Minutes of the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. Accessed 11/18/16. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM527701.pdf. Accessed 11/18/16.
3. Deshpande G, Gill A. Cardiac arrest following naloxone in an extremely preterm neonate. Eur J Pediatr 2009;168:115-117. DOI 10.1007/s00431-008-0720-3
4. Gibbs J, Newson T, Williams J, Davidson DC. Naloxone hazard in infant of opioid abuser. Lancet 1989;2(8655):159-160.

6 APPENDICES

6.1 APPENDIX A. FDA APPROVED NALOXONE PRODUCTS

Product Name	Active Ingredient	(A)NDA	Initial Approval	Strength	Dosage Form/Route
Narcan	Naloxone hydrochloride	N208411	11/18/15	4 mg/spray	Spray, metered; Nasal
Evzio	Naloxone hydrochloride	N205787 N209862	04/03/14 10/19/16	0.4 mg/ 0.4 mL 2 mg	Solution; Intramuscular, Subcutaneous Injectable; Injection
Naloxone	Naloxone hydrochloride	A070299	10/22/85	0.4 mg/mL	Injectable; Injection
Multiple	Naloxone hydrochloride	A070172 A070254 A070256 A070257 A070639 A072076 A204997 A205014	04/18/86 01/07/87 01/07/87 01/07/87 01/17/86 03/24/88 03/06/14 06/29/16	0.4 mg/mL 0.4 mg/mL 0.4 mg/mL 0.4 mg/mL 0.4 mg/mL 1 mg/mL 0.4 mg/mL 0.4 mg/mL	Injectable; Injection

6.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.3 APPENDIX C. EXCLUDED CASE OF INTEREST

Naloxone overdose

FAERS case #6689517, France, Received June 2008
A 3-day-old female newborn received morphine 0.85 mg/kg/day and underwent accidental extubation. One hour later, the baby was sleeping deeply and began to have dyspnea, increased oxygen requirements, wheezing and desaturation of 78%. Narcan 1.5 mL, from a special neonatology vial concentrated to 0.04 mg/2 mL, was prescribed to be given over two minutes. Unfortunately, the pharmacy cupboard contained Narcan concentrated to 0.4 mg/mL and the baby received 20 times the prescribed dose accidentally. Tachycardia, hypertension, sweating, hypersialorrhea and agitation occurred. Within one hour and thirty minutes after the administration of morphine 0.05 mg, there was progressive improvement. The next day, the pediatrician reported several yawns and sneezes and suspected persistent signs of "weaning" had begun. By the ninth day of admission, the baby's EEG was normal. A cerebral MRI on the eleventh day of admission was also reported as normal.

Reviewer's comment: The adverse events of tachycardia, hypertension, sweating, hypersialorrhea, and agitation are consistent with opioid withdrawal symptoms which may have been abruptly precipitated by the naloxone overdose. Of note, the newborn received one dose of morphine (her weight was not reported).

6.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR THE THREE FAERS CASES

Line	FAERS Case Number	Version Number	Manufacturer Control Number
1	6070713	1	NARC20050003
2	6907364	1	AU-ROXANE LABORATORIES, INC.-2009-RO-00118RO
3	6689517	1	NARC20080002

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/s/

CHAITALI C PATEL
12/14/2016

SARA L CAMILLI
12/14/2016

M E M O R A N D U M

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

DATE: December 13, 2016

TO: Sharon Hertz, M.D.
Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Office of New Drugs (OND)

Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Yiyue Zhang, Ph.D.
Visiting Associate
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Stanley Au, Pharm.D., BCPS
Team Lead (Acting)
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, CA.

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) inspe analytical portion of in vivo bioavailability (BA) Studies (b) (4) (b) (4) submitted to NDA 208969, (b) (4) (b) (4) We issued a six-item Form FDA 483 to Amphastar Pharmaceuticals at the conclusion of the inspection. The final classification is Voluntary Action Indicated

(VAI). After review of the study conduct, inspectional findings and the firm's response, we recommend that the analytical data submitted from all five studies should be accepted for further Agency review.

(b) (4)

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(b) (4)

Conclusions:

After reviewing the EIR, inspectional findings and the firm's response to Form FDA 483, we fou

(b) (4)

(b) (4)

Yiyue Zhang, Ph.D.
DNDBE, OSIS

Stanley Au, Pharm.D., BCPS
DGDBE, OSIS

Final Classification:

Analytical Site

VAI: Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, CA
FEI: 3002936358

Attachments:

Attachment 1: Form FDA 483 "Inspectional Observations"
Attachment 2: Amphast the Form FDA 483
Attachment 3: Method (b) (4) Section 5.0 Procedure
Attachment 4: Investigation report of the potential sample misplacement

CC:
OTS/OSIS/Kassim/Taylor/Haidar/Fenty-Stewart/Nkah/Miller/Kadavil/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang
OTS/OSIS/DGDBE/Cho/Murphy/Choi/Skelly/Au
OND/DAAAP/Hertz

Draft: YZ 10/24/2016, 11/4/2016, 11/21/2016, 11/29/2016, 12/9/2016
Edit: SA 11/01/16, 11/29/16, 11/30/16; RCA 11/8/16, 11/23/2016, 11/30/2016; AD 11/18/2016; CB 12/01/2016, 12/8/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Amphastar Pharmaceuticals, Inc., Rancho Cucamonga, CA

OSIS BE#: 7199
FACTS: 11652917

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CHARLES R BONAPACE
12/13/2016

M E M O R A N D U M

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

DATE: November 28, 2016

TO: Sharon Hertz, MD
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs

AND

Dale P. Conner, Pharm.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Elise A. Murphy
Deputy Director (Acting)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of Clinical Site Inspection at the site: West Coast Clinical Trials, LLC (WCCT), Cypress, CA

covering the following applications and complaint:

NDA 208969, Naloxone Hydrochloride Nasal Spray, sponsored by **Amphastar Pharmaceuticals, Inc.**

(b) (4)

Inspection Summary:

The inspection was conducted at West Coast Clinical Trials, LLC (WCCT), Cypress, CA to cover study (b) (4), supporting Naloxone Hydrochloride Nasal Spray NDA 208969, (b) (4)

(b) (4)

This reviewer recommends data from these studies should be accepted for further agency review.

Inspected studies:

The inspection audited the clinical portion of the following studies:

Application #: **NDA 208969**
Study #:
Study Title: (b) (4)

Dates of Study Conduct: (b) (4)

Application #:
Study #:
Study Title: (b) (4)

Dates of Study Conduct:

The inspection of the clinical portion of studies (b) (4) (**NDA 208969**) and (b) (4) was conducted by ORA Investigators Lakecha N. Lewis and Comyar Shoghi at WCCT, Cypress, CA from October 6 to October 14, 2016. The inspection included a review of study protocols and amendments, Forms FDA 1572 Statement of Investigator, records of subjects' informed consent forms, subject eligibility documents, screening and enrollment logs, delegation logs, IP/study drug receipt, storage and accountability logs, administration, dosing and shipment records, IRB approvals and correspondences, sponsor/monitor correspondence, laboratory result reports, and subjects' source records.

No significant objectionable conditions or findings were observed. No Form FDA 483 Inspectional Observations was issued to the firm.

Complaint:

(b) (4)

OSIS Assessment:

Form FDA 483 Inspectional Observations was not issued to the firm. The inspection found no evidence to support the misconduct alleged by the complaint. In this reviewer's opinion, data from these studies should be considered reliable.

Recommendations:

This reviewer recommends that data from these studies (b) (4) should be accepted for further agency review.

Complaint file (b) (4) should be closed.

Final Classifications:

NAI: West Coast Clinical Trials, LLC (WCCT), Cypress, CA (**FEI: 3006237846)**

Xingfang Li -S

Digitally signed by Xingfang Li -S
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OSIS/DGDBE/Cho/Murphy/Skelly/Choi/Au/Li
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CDER/OGD/OB/Conner

Draft: XFL 11/28/2016
Edits: MFS 11/29/2016; EAM 11/29/2016
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/West Coast Clinical Trials, LLC (WCCT) Cypress, CA

OSI file #: [redacted] (b) (4) (NDA 208969); [redacted] (b) (4) (complaint)
FACTS: 11610574

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/s/

XINGFANG LI
12/02/2016

MICHAEL F SKELLY
12/02/2016

ELISE A MURPHY
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