

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215487Orig1s000

OTHER REVIEW(S)

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: January 24, 2024

Requesting Office or Division: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Application Type and Number: NDA 215487

Product Name, Dosage Form, and Strength: Rezenopy (naloxone hydrochloride) nasal spray, 10 mg

Applicant/Sponsor Name: Summit Biosciences Inc.

TTT ID #: 2023-4175-2

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 labels, carton labeling, quick start guide (QSG), and Instructions for Use (IFU) on January 11, 2024, and prescribing information (PI) received on January 19, 2024, for Rezenopy. Additionally, the Applicant submitted revised device foil peel label via email on January 22, 2024, for Rezenopy. Subsequently, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels, device foil peel label, carton labeling, QSG, IFU, and PI for Rezenopy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.^{a,b}

2 DISCUSSION

In our previous review, we recommended DAAP consider having the Applicant add the established name “naloxone hydrochloride” after the proprietary name placeholder, TRADENAME, on the back container label to be in accordance with 21 CFR 201.10(g)(1).^b We

^a Birkemeier D. Label and Labeling Review for naloxone hydrochloride (NDA 215487). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 SEP 9. TTT ID No.: 2023-4175.

^b Birkemeier D. Label and Labeling Review Memo for naloxone hydrochloride (NDA 215487). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 SEP 9. TTT ID No.: 2023-4175-1.

confirmed via email with our DAAP colleagues that they intend to ask the Applicant to include the established name on the back container label as part of the approval letter.

3 CONCLUSION

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

APPENDIX A. LABEL AND LABELING RECEIVED ON JANUARY 11, 2024, JANUARY 19, 2024, AND JANUARY 22, 2024

- Quick Start Guide (QSG) (Image not shown) available from:
<\\CDSESUB1\EVSPROD\nda215487\0034\m1\us\114-labeling\draft\carton-and-container\qsg-ifu-package-insert-art-5.doc>
- Instructions for Use (IFU) (Image not shown) available from:
<\\CDSESUB1\EVSPROD\nda215487\0034\m1\us\114-labeling\draft\carton-and-container\draft-carton-container-labels-ifu-pi-art.docx>
- Prescribing Information (PI) (Image not shown) available from:
<\\CDSESUB1\EVSPROD\nda215487\0036\m1\us\114-labeling\draft\carton-and-container\draft-labeling-text-pi-tracked.docx>



2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAMON A BIRKEMEIER
01/24/2024 02:50:00 PM

VALERIE S VAUGHAN
01/24/2024 02:56:15 PM



**DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM**

Date	12/22/2023		
To:	Anika Lalmansingh		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	Choose an item.
From	Dunya Karimi OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Division Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA 215487 , Naloxone ICC2300431 Case 00920016		
Recommendation	Filing Recommendation Date: 7/7/2023 ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 8/24/2023 ☐ 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: 12/22/2023 ☒ 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)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 215487
Sponsor	Summit Biosciences, Inc.
Drug/Biologic	Naloxone
Indications for Use	emergency treatment of known or suspected opioid [REDACTED] (b) (4) [REDACTED] overdose
Device Constituent	Nasal Spray
Related Files	

Review Team	
Lead Device Reviewer	<i>Dunya Karimi</i>

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 <u>Notes</u>
	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	Defer to DMPEA
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

Summit Biosciences, Inc. is requesting approval of Nalaxone. 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:

A review of the device-related information in the submission.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. 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

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
Naloxone	emergency treatment of known or suspected opioid (b) (4)
Nasal Spray	overdose Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
001	
0031	

4. DEVICE DESCRIPTION

4.1. Device Description

Naloxone Nasal Spray is a pre-filled and pre-assembled combination product, and it is designed for a single use. The container closure system for Naloxone Nasal Spray is a standard, non-customized unit dose system comprised of a vial, plunger (stopper), container holder (vial holder) and actuator assembly (containing an actuator, spray pin, and cannula).

Table 1: Container Closure Component Information

Component	Material Type	Drawing Reference	Summit Part Number	Manufacturer	Type III DMF #
Vial	Clear, type (b) (4) glass vial with (b) (4)	(b) (4)			
Plunger (Rubber Stopper)	(b) (4)				
Container Holder (Vial Holder)	(b) (4)				
Actuator Sub-Assembly	(b) (4)				

Figure 1: Overview of Components and Assembly (Provided by (b) (4)



Figure 2: Function of the Unit Dose Delivery System (Provided by



4.2. Steps for Using the Device

1. Check for signs of opioid overdose
2. Position person
3. Remove device
4. Hold device - Hold with your index and middle fingers on either side of the nozzle and your thumb on the bottom of the plunger (Do not apply any pressure until you are ready to give the dose)
5. Prepare to give Naloxone nasal spray - Tilt the person's head back and provide support with your hand. Insert the nozzle tip all the way into one nostril
6. Give Naloxone nasal spray - Push the plunger hard and all the way in to give the dose. Remove from nostril after dosing. Push Plunger
7. Get emergency help
8. Turn to recovery position and monitor
9. Give second dose if necessary and monitor (with a new nasal spray)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The device description is acceptable.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

CDRH performed Filing Review	☒

CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review

5.1. Filing Review Checklist

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability	X		
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors			X- defer to DMEPA
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment

5.2. Facilities Information

Firm Name: Summit Biosciences Inc.

Address:	Coldstream Research Campus 1513 Bull Lea Road Lexington, KY 40511
FEI:	3007577023
Responsibilities:	Summit Biosciences Inc. will be manufacturing, processing, packaging, labeling and testing (raw material, in-process, finished product and stability testing) the Naloxone Hydrochloride Nasal Spray, 10 mg
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date. . The inspection covered Choose an item. and was classified Choose an item. ☒ 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 <u>is required</u> 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 <u>is not required</u> because Choose an item.	

5.3. 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. Given that the final combination product is considered emergency use and has the possibility to be used for a vulnerable population and that if the product is not delivered correctly, the person suffering from an overdose may expire, there is a high risk of cGMP issues.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☒ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	
Site(s) needing inspection: Summit Biosciences Inc.	
<u>Reviewer Comments</u> N/A	
Refuse to File Deficiencies: ☐ Yes ☒ No ☐ N/A	
74-Day Letter Deficiencies: ☐ Yes ☒ No ☐ N/A	

LABELING

5.5. 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 – Defer to DMEPA
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

5.6. 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. Further analysis of the Instructions for Use is deferred to DMEPA.

5.7. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> The device labeling is acceptable.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

6. DESIGN CONTROL SUMMARY

6.1. 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

6.2. Design Inputs and Outputs

Essential Performance Requirements

<u>Design Inputs (Essential Performance Requirement)</u>	<u>Design Outputs (Specification)</u>
Pump Delivery (Spray Weight)	(b) (4)
Spray Pattern	
Plume Geometry	
Droplet Size Distribution	
Spray Content Uniformity	
Actuation Force (Break/Glide Force)	

Reviewer Comments

The Essential Performance Requirements (EPRs) outlined for the Naloxone Nasal Spray 10mg 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:

- 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.*
- 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).*
- 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 non 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.*

The pump delivery specification is outside of normal limits for other Naloxone products. The acceptability of this specification has been deferred to CDER. An email was sent and communicated to the clinical team to make them aware of the issue. The clinical team followed-up asking if whether there is a reason that the spec is so wide, and whether the testing results are in line with those specs. CDRH LR clarified that the reason for the wide range for the spec is unclear but that the results fell within the specified range (results are closer to what we typically see for naloxone products), but again, the reason for the spec being so high is unclear. CDRH was then requested to send an IR to request the specification be changed and we sent the following communication to CDER:

I discussed with my AD and again, we defer the acceptability of this spec to the clinical team. If they believe the specification should be more narrow, I think it would be best for them to communicate the request to the sponsor given the issue would be of one that raises concerns with the intended therapy and not performance of the device. Because the device performs as the sponsor is stating, we cannot request for a change in this specification from the CDRH end. If an IR does get sent and the sponsor does change the specification, CDRH would be happy to look at updated device performance data they provide to support the change to the spec, but again, the actual request for change should come from the clinical team if they deem it appropriate.

6.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	n/a
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	n/a
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	n/a

Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Defer to DMEPA

6.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> The design control is acceptable.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

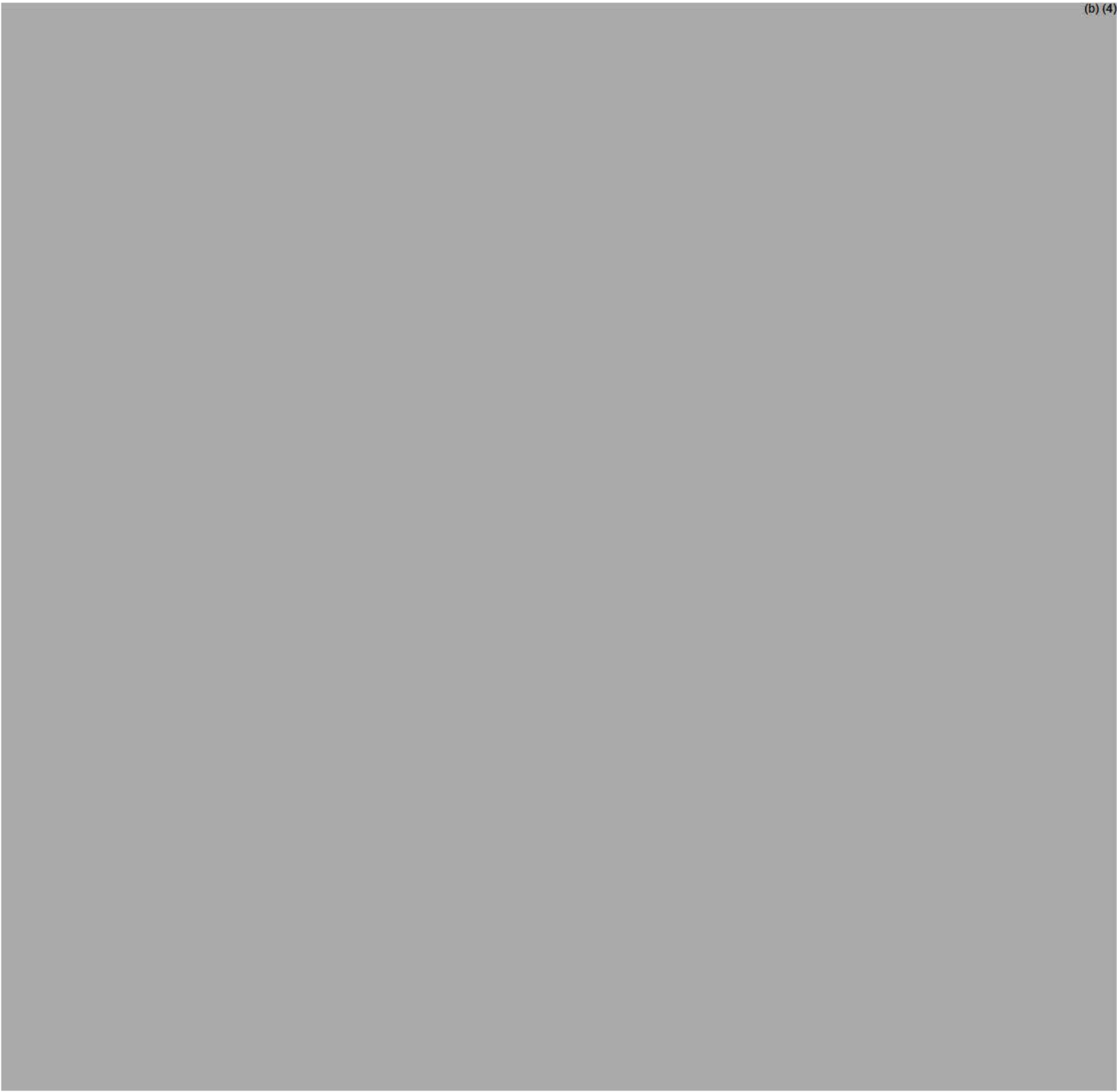
7. RISK ANALYSIS

7.1. Risk Management Plan

A risk assessment was performed for Naloxone HCl 10 mg Nasal Spray (Naloxone Nasal Spray) to identify any areas that require mitigation or further development activities prior to process validation and commercialization. The purpose of this document is to identify risks associated with the device due to variables that relate to device components, formulation, and user/patient knowledge.



(b) (4)



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.

In response to the IRs below, the sponsor provided an updated FTA which addresses all of the elements listed above. This is acceptable.

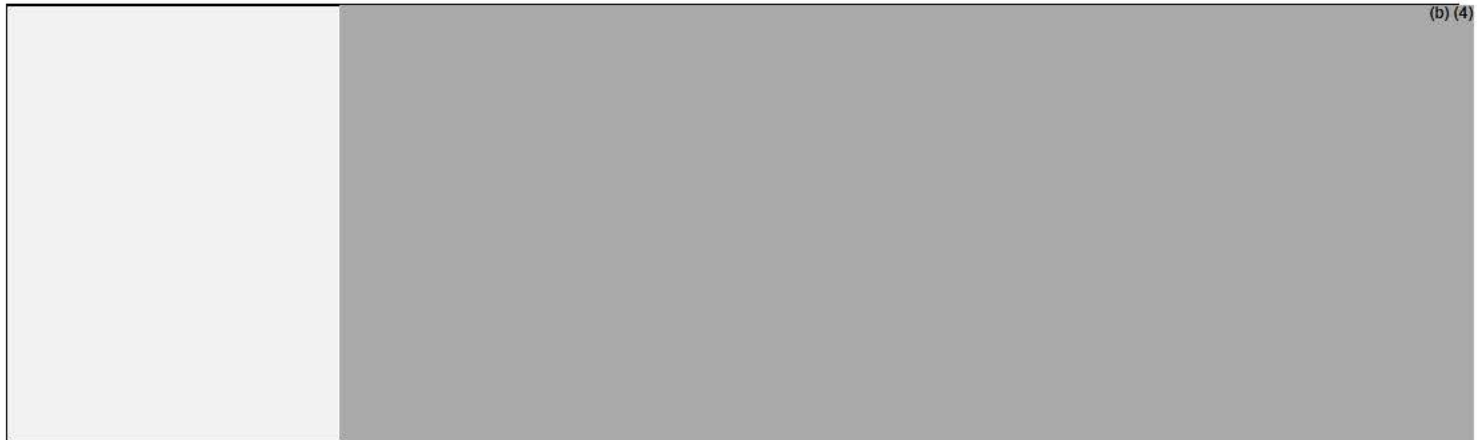
7.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> The risk analysis is acceptable.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #1	(b) (4)	
Sponsor Response		

Reviewer Comments	All risk management reports were provided for review. The reports adequately mitigate risks associated with the device as far as possible and include justifications for risks assessed as ALAP. This is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #2	(b) (4)	
Sponsor Response		



Reviewer Comments

The sponsor provided the following updates to their FTA:

- A top-failure mode was identified as “failure to deliver complete intended dose”.
- the probability of each failure mode demonstrating a reliability of (b) (4)% that traces up to the top-level failure mode
- The FTA includes the failure descriptions outlined in the uFMEA, dFMEA and pFMEA indicating the design and manufacturing elements are all considered.

(b) (4)

	The reliability specifications for the device is (b) (4). This is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

8. DESIGN VERIFICATION REVIEW

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Pump Delivery (Spray Weight)			(b) (4) Y	Y
Spray Pattern			Y	Y
Plume Geometry			Y	Y
Droplet Size Distribution			Y	Y
Spray Content Uniformity			Y	Y
Actuation Force (Break/Glide Force)			Y	Y

Reviewer Comment See table below.

8.1.2. Verification of Design Inputs Evaluation

<u>Design Input</u>	<u>Design Output</u>	<u>Verification Method</u>	<u>Results/Deviations</u>	<u>Adequately Verified (Y/N)</u>	<u>Validated through Clinical Human Factors or Other</u>
Pump Delivery (Spray Weight)			(b) (4)	N – unclear specifications (inconsistent units of measurement for the specification listed and the results provided), no justification for sample size (unclear C/R to determine adequacy of sample size), unclear C/R. See IRs below. RESOLVED Updated results table provided to include pump delivery in (%). Results show the device	n/a within benchmark values

				(b) (4) adequately conforms to the specification. This is acceptable.	

		(b) (4)	
Spray Pattern		N – See IRs below. RESOLVED	n/a within benchmark values
Plume Geometry		N – unclear specifications (inconsistent between two sets of test reports provided), no justification for sample size (unclear C/R to determine adequacy of sample size),	n/a

		(b) (4) unclear C/R. See IRs below. RESOLVED Updated results table provided to report the results consistently (plume width (mm) and plume angle (°)). Results show adequately conform to the specification. This is acceptable.	

		(b) (4)	
Droplet Size Distribution		N – See IRs below. RESOLVED	n/a within benchmark values

		(b) (4) In response to the IR below, an updated test report was provided to include droplet size distribution. Sample size, C/R and complete results are included. This is acceptable.	
Spray Content Uniformity		N – See IRs below. RESOLVED In response to the IR below, an updated test report was provided to include spray content uniformity. Sample size, C/R and complete results are included. This is acceptable.	n/a within benchmark values

Actuation Force (Break/Glide Force)	(b) (4)	N – See IRs below. RESOLVED In response to the IR below, an updated test report was provided to include droplet size distribution. Sample size, C/R and complete results are included. This is acceptable.	n/a within benchmark values

Reviewer Comment

The device verification is incomplete. The sample sizes are unjustified, unclear C/R, inconsistencies between the specs and the results (i.e. different units of measurement and inconsistencies of specifications between different data sets). No verification test reports found for spray pattern, droplet size distribution, spray content uniformity and actuation force. **See IRs below. RESOLVED**

In response to the IRs below, the sponsor provided updated test reports to clarify sample sizes, C/R and results (see table above). All updates demonstrate adequate performance of the nasal spray. This is acceptable.

A follow-up IR was sent to the sponsor to request further clarification on the test methods for dose delivery testing, specifically to request information on the angle of delivery during the test (see IR table below). The sponsor clarified that the test was done at 0° and 45° which is within the range needed to deliver the dose to a patient laying down. This is acceptable.

8.1.3. *Evaluation of Test Methods*

Title:	Reliability Study

Scope/Objective & Acceptance Criteria: To demonstrate reliability of Summit Biosciences' Naloxone HCl 10 mg Unit Dose Nasal Spray Device through summary of (1) extensive testing of combination product that has been exposed to foreseeable , worst-case conditions through deliberate mechanical and environmental stressors as outlined by EPI I-SN-00 Naloxone HCl IO mg Unit Dose Nasal Spray Device Reliability Study and by (2) the results of a Fault Tree Analysis conducted for both a system level failure as well as each identified Essential Performance Requirement.

Methods

Table 1: Essential Performance Requirement Reliability Criteria

Essential Performance Requirement (EPR)	Sub-Requirement	Lower Specification Limit	Upper Specification Limit	Reliability Requirement (Coverage at 95% Confidence)
Successful Activation	N/A	(b) (4)		
Pump Delivery (Spray Weight)	N/A			
Spray Pattern	Ovality ¹			
	D _{max}			
Droplet Size Distribution (DSD)	D ₅₀			
	Span			
	(b) (4)			
Activation Force	N/A	(b) (4)		

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(b) (4)

Table 8: FTA Calculated Reliability

EPR	Acceptance Criteria (Reliability%)	Calculated Reliability %	Acceptance (Pass / Fail)
Successful Activation		(b) (4)	Pass
Pump Delivery		Pass	
Activation Force		Pass	
Droplet size Distribution		Pass	
Spray Pattern		Pass	

Conclusions/ Reviewer Comments:

The reliability test is adequate. All results meet the outlined specifications and demonstrate an acceptable C/R of (b) (4)% reliability for the EPRs. This is acceptable.

Acceptable:

Yes No

Title:	Stability Test
Scope/Objective & Acceptance Criteria:	Three (3) representative lots of Naloxone HCl 10 mg Nasal Spray Drug Product were placed on stability. For Lot CSNB1903A, stability studies SP09-SN19-00 Stability Protocol – Naloxone HCl 10 mg Unit Dose and SP09-SN19-02 Stability Protocol – Naloxone HCl 10 mg Unit Dose were initiated 09/27/2019 and 10/11/2019, respectively. Stability study SP09-SN19-03 Stability Protocol – Registration Stability Naloxone HCl 10 mg Unit Dose was initiated on 10/25/2019 for batches RSNB1904A and RSNB1905A. Based on completion of the long-term stability study which resulted in a conforming drug product, a shelf life of 36 months is proposed in accordance with ICH Q1E for the drug product in the commercial container closure system.
Methods	(b) (4)

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Conclusions/ Reviewer Comments:	Unclear sample sizes and C/R. See IRs below. RESOLVED In response to the IR below, the sponsor provided updated stability tables that indicate sample sizes for each test. This is acceptable.
Acceptable:	☒ Yes ☐ No

Reviewer Comment

Insert Additional Design Verification Table

8.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #3	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	(Sequence 0027 module 3.2.P.8 report <i>DR-11-SN-01</i>) The sponsor makes an assertion [REDACTED] (b) (4) [REDACTED] We do not agree with this assessment as it contradicts information provided in the Nasal Spray Guidance Document <i>Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation</i> . However, the sponsor still provided updated device verification reports to include results for spray pattern, droplet size distribution, spray content uniformity and actuation force. The report includes sample size, C/R and results for each test demonstrating adequate performance of the device. This is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #4	(b) (4)	

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	(b) (4)
Reviewer Comments	Updated test reports were provided to clarify the results for Pump Delivery and Plume Geometry (Sequence 0027 module 3.2.P.7 report <i>PR10-SN20-00</i>). The reports included results with consistent units of measure and adequately demonstrate performance of the device per the specifications outlined. The reports also include sample size, C/R and complete statistical results. This is acceptable. The response to IR3 adequately clarifies sample size, C/R and data analysis methods for all EPRs (see tables above). This is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #5	(b) (4)	
Sponsor Response	(b) (4)	

Reviewer Comments	Both reliability and stability reports were updated to include C/R and sample sizes for each EPRs (see performance tables above). This is acceptable.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: 12/20/2023	Date/Sequence Received: 12/22/2023
Information Request #5	(b) (4)	
Sponsor Response		
Reviewer Comments	An IR was sent to the sponsor to request further clarification on the test methods for dose delivery testing, specifically to request information on the angle of delivery during the test (see IR table below). The sponsor clarified that the test was done at 0° and 45° which is within the range needed to deliver the dose to a patient in an emergency situation. This is acceptable.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

Add Additional Information Request

No Additional Information Requests – Finalize Design Verification Review Section

8.3. Discipline Specific Sub-Consulted Review Summary

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

9. CLINICAL VALIDATION REVIEW

9.1. Review of Clinical Studies Clinical Studies

- There is no device related clinical studies for review
 There are clinical studies for review

10. HUMAN FACTORS VALIDATION REVIEW

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

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

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

Reviewer Comments

One Pre-Approval Inspection required. See above.

Facilities Review Conclusion

The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.

Yes

No

11.2. Quality Systems Documentation Review

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

11.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

(b) (4)



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

11.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

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	Firm(s):	(b) (4)

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

Reviewer Comments
 The GMP compliance information provided by the sponsor is acceptable.

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

11.2.3. Corrective and Preventive Action Review

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

(b) (4)

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 CAPA information provided by the sponsor is acceptable.

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.

Yes

No

11.3. 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 <u>release testing activities</u> :	Acceptable (Y/N/NA)
<u>Spray Pattern</u>	The EPRs outlined to the left are included in the release testing per the control strategy documents provided by the sponsor	Y
Droplet Size Distribution		Y
Pump Delivery		Y
Successful activation		Y
Activation Force		Y

Reviewer Comments

Cannot locate GMP information or control strategy information. See IRs below. **RESOLVED**

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

11.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☒ N/A
Reviewer Comments The Facilities and Quality System information is acceptable.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #6	(b) (4)	

Sponsor Response	(b) (4)
Reviewer Comments	The final response to this IR was received on 12/21/2023. The data provide (see above) was adequate to summarize the cGMP and CAPA procedures.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #7	(b) (4)	
Sponsor Response		



Reviewer Comments	In the final response to this IR (received on 12/21/2023), the sponsor provided information to confirm that all EPRs are included in the release testing per the control strategy described above. This is adequate.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

<<END OF REVIEW>>

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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: December 20, 2023

Requesting Office or Division: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Application Type and Number: NDA 215487

Product Name, Dosage Form, and Strength: naloxone hydrochloride nasal spray, 10 mg

Applicant/Sponsor Name: Summit Biosciences Inc.

TTT ID #: 2023-4175

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 prescribing information (PI), quick start guide (QSG), and instructions for use (IFU) received on November 29, 2023, and container labels, outer device foil label, and carton labeling received on December 5, 2023, for naloxone hydrochloride. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised PI, QSG, IFU, container labels, outer device foil label, and carton labeling naloxone hydrochloride (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and during a human factors validation study report review.^{a,b}

2 CONCLUSION

The revised PI, QSG, IFU, container labels, outer device foil label, and carton labeling are acceptable from a medication error perspective. However, we note that while not a medication error concern, the revised container label does not include the established name, naloxone

^a Birkemeier D. Label and Labeling Review for naloxone hydrochloride (NDA 215487). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 SEP 22. TTT ID No.: 2023-4175.

^b Oguntimein M. Human Factors Validation Study Results Report Review for naloxone hydrochloride (NDA 215487). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 4. TTT ID No.: 2023-4168.

hydrochloride, on the back container label following the tradename placeholder. Thus, we consulted our colleagues in the Office of Unapproved Drugs and Labeling Compliance (OUDLC) who agreed the product would be considered misbranded for failure to comply with the labeling requirement that the established name accompanies the proprietary name each time it appears on the container label as described in 21 CFR 201.10(g)(1).

3 RECOMMENDATIONS FOR THE DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

We recommend the Division considers the following recommendation prior to approval of this NDA:

- A. Add the established name "naloxone hydrochloride" after the proprietary name placeholder, TRADENAME, on the back container label to be in accordance with 21 CFR 201.10(g)(1).

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 29, 2023 AND DECEMBER 5, 2023

- Quick start guide (image not shown) available via:
<\\CDSESUB1\EVSPROD\nda215487\0028\m1\us\114-labeling\draft\carton-and-container\qsg-ifu-package-insert-art-5.doc>
- Instructions for use (image not shown) available via:
<\\CDSESUB1\EVSPROD\nda215487\0028\m1\us\114-labeling\draft\carton-and-container\draft-carton-container-labels-ifu-pi-art.docx>
- Prescribing information (image not shown) available via:
<\\CDSESUB1\EVSPROD\nda215487\0028\m1\us\114-labeling\draft\carton-and-container\draft-labeling-text-pi.docx>
- Response to container label and carton labeling comments available via:
<\\CDSESUB1\EVSPROD\nda215487\0029\m1\us\114-labeling\draft\labeling\draft-labeling-text-carton-comments.pdf>



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/s/

DAMON A BIRKEMEIER
12/20/2023 04:13:28 PM

VALERIE S VAUGHAN
12/20/2023 04:27:27 PM

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

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

Memorandum

Date: October 19, 2023

To: Zachary Dezman, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Rachel Jang, 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 TRADENAME (naloxone hydrochloride) nasal spray

NDA: NDA 215487

In response to DAAP's consult request dated May 15, 2023. OPDP has reviewed the proposed product labeling (PI), Patient Package Insert (PPI), Instructions for Use (IFU), Quick Start Guide (QSG) and carton and container labeling for the original NDA submission for TRADENAME (naloxone hydrochloride) nasal spray.

PI/PPI/IFU/QSG:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 5, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU/QSG, and comments were sent under separate cover on October 18, 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 March 24, 2023. OPDP recommends that the sponsor update the IFU/QSG information included on the carton labeling, in a manner consistent with the revisions to the IFU/QSG provided in OPDP/DMPP's combined review.

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

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/s/

LATOYA S TOOMBS
10/19/2023 11:54:25 AM

**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: October 18, 2023

To: Rachel Jang, PharmD
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),
Instructions for Use (IFU), and Quick Start Guide (QSG)

Drug Name (established name): TRADENAME (naloxone hydrochloride)

Dosage Form and Route: Nasal Spray

Application Type/Number: NDA 215487

Applicant: Summit Biosciences Inc.

1 INTRODUCTION

On March 24, 2023, Summit Biosciences Inc. submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 215487 for TRADENAME (naloxone hydrochloride) Nasal Spray. The Reference Listed Drug (RLD) is NARCAN (Naloxone Hydrochloride Injection, USP) NDA 016636. The proposed indication for TRADENAME (naloxone hydrochloride) Nasal Spray is for the emergency treatment of known or suspected opioid (such as hydrocodone, oxycodone, fentanyl, and morphine) overdose, as manifested by respiratory and/or central nervous system depression.

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 May 15, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), Instructions for Use (IFU) and Quick Start Guide (QSG) for TRADENAME (naloxone hydrochloride) Nasal Spray.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU and QSG was completed on September 22, 2023.

2 MATERIAL REVIEWED

- Draft TRADENAME (naloxone hydrochloride) Nasal Spray PPI, IFU and QSG received on March 24, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 5, 2023.
- Draft TRADENAME (naloxone hydrochloride) Nasal Spray Prescribing Information (PI) received on March 24, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 5, 2023.
- Approved NARCAN (naloxone hydrochloride) nasal spray comparator labeling dated March 27, 2023.
- 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.

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 APFont to make medical information more

accessible for patients with vision loss. We reformatted the PPI, IFU, and QSG document using the Arial font, size 10.

In our collaborative review of the PPI, IFU, and QSG we:

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

4 CONCLUSIONS

The PPI, IFU, and QSG are 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, IFU, and QSG 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, IFU, and QSG.

Please let us know if you have any questions.

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/s/

RUTH I MAYROSH
10/18/2023 12:35:39 PM

LATOYA S TOOMBS
10/18/2023 01:20:17 PM

LASHAWN M GRIFFITHS
10/18/2023 01:46:03 PM

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)

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

Date of This Review:	September 22, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215487
Product Name, Dosage Form, and Strength:	naloxone hydrochloride nasal spray, 10 mg
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Summit Biosciences Inc.
FDA Received Date:	March 24, 2023
TTT ID #:	2023-4175
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for naloxone hydrochloride nasal spray, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed naloxone hydrochloride prescribing information (PI), quick start guide (QSG), instructions for use (IFU), container labels, outer device foil label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 215487 is a 505(b)(2) NDA and the listed drug product is Narcan (naloxone hydrochloride injection), NDA 016636.

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
Other	E – N/A
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 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), quick start guide (QSG), instructions for use (IFU), container labels, outer device foil label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Summit Biosciences Inc.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The review team requested we opine on how to best convey to end-users that, while this is a higher-strength 10 mg naloxone hydrochloride nasal spray product, it is not expected to provide greater efficacy as compared to 8 mg naloxone hydrochloride nasal spray products.		We recommend including language such as “Intranasal doses of 10 mg of TRADENAME produced plasma levels similar to that of 8 mg doses of other naloxone hydrochloride nasal spray products. Both 8 mg and 10 mg doses have been shown to be efficacious in reversing the effects of opioid overdose.” Additionally, we recommend including a reference to the relevant information in Section 12 <i>Clinical Pharmacology</i> within Section 2.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The package type term is missing.	Per USP <659> <i>Packaging and Storage Requirements</i> , the current terminology for your product is “unit-dose”.	We recommend revising the statement in Section 3 <i>Dosage Forms and Strengths</i> to read “Nasal spray: 10 mg of naloxone hydrochloride per device. Each unit-dose nasal spray delivers a single spray containing 10 mg of naloxone hydrochloride.”
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	It is unclear which NDC # is being referred to in the statement “TRADENAME Nasal Spray 10 mg is supplied as a carton containing two (2) blister packages (NDC XXXX-	The product is intended to be dispensed as an intact carton containing two devices.	When the NDC is finalized, we recommend ensuring the NDC # listed corresponds to the NDC # corresponding to the carton of two devices as opposed to the NDC for the individual device.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	XXX-XX) each with a single spray device.”		

5 RECOMMENDATIONS FOR SUMMIT BIOSCIENCES INC.

Note that additional label and labeling comments may be forthcoming based on our evaluation of your human factors validation study results.

Table 3. Identified Issues and Recommendations for Summit Biosciences Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	As currently presented, the route of administration is missing from the container label.	The route of administration statement is considered to be “critical information.” See our <i>Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> for more information. ^a To mitigate the risk of medication errors involving wrong route of administration, the route of administration statement should be prominently displayed on the PDP.	If space permits, we recommend including the statement “For use in the nose only” on the container label.
2.	As currently presented, the established name does not follow the proprietary name	The proprietary name and established along with the product strength, route of administration, and	We recommend revising the container label so that the established name follows the proprietary name placeholder

^a 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 3. Identified Issues and Recommendations for Summit Biosciences Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	placeholder "TRADENAME" and is not prominent on the container label.	warnings or cautionary statements (if any) should be the most prominent information on the principal display panel (PDP).	"Tradename" followed by the dosage form. To make room for the established name, consider relocating the NDC to allow for the established name to follow the iRADENAME. Additionally, to conserve space on the small container label, we recommend removing the duplicate [REDACTED] (b) (4) [REDACTED] on the side of the PDP of the container label.
Carton Labeling			
1.	As currently presented, the route of administration is listed as [REDACTED] (b) (4)	This statement can be improved to increase comprehension by lay users.	We recommend revising this statement to read "For use in the nose only".
2.	There is a placeholder for serialization information, but it is not clear if this contains the full human-readable portion of the product identifier information.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes. ^b The drug package label must include the product identifier information (i.e., the NDC, serial number, lot number,	Please confirm the serialization area contains the human-readable portion of the product identifier information. Additionally, we recommend the expiration date format on the carton labeling match the expiration date format on the container label.

^b Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers. 2021. Available from: <https://www.fda.gov/media/116304/download>.

Table 3. Identified Issues and Recommendations for Summit Biosciences Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		and expiration date) in both the human-readable form and machine-readable 2D data matrix barcode format.	
3.	The terminology (b) (4) within the statement of dosage is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage to read, "Dosage and Administration: see Prescribing Information".
4.	As currently presented, the package type term is missing from the carton labeling.	Per USP <659> <i>Packaging and Storage Requirements</i> , the correct terminology for your product is "unit-dose".	Revise the statement "2 Nasal Spray Devices" to include the package type term "unit-dose". For example, "2 Unit-dose Nasal Spray Devices".
Device Foil Peel (Blister Pack) Labeling			
1.	As currently presented, the route of administration is listed as (b) (4)	This statement can be improved to increase readability and comprehension by lay users.	We recommend revising this statement to read "For use in the nose only".
2.	We note that the carton labeling contains the statement "Do NOT remove from blister or test before use". However, no similar statement is present on the device foil peel labeling.	We note that each device administers a single spray equivalent to a single 10 mg dose. Therefore, an end user attempting to test the device prior to use could result in no dose being available for the patient.	We recommend adding the following statement to the device foil peel label: "Do NOT test device before use"
Quick Start Guide (QSG)			
1.	As currently presented, the route of administration is listed as (b) (4)	This statement can be improved to increase readability and	We recommend revising this statement to read "For use in the nose only".

Table 3. Identified Issues and Recommendations for Summit Biosciences Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		comprehension by lay users.	
2.	We note the QSG contains the statement (b) (4)	We note the phras (b) (4) could misleadingly cause end users (b) (4)	We recommend revising this statement into two statements to read "Do not unpack TRADENAME Nasal Spray until ready to use. Do NOT test TRADENAME Nasal Spray before use."
Instructions for Use (IFU)			
1.	As currently presented, the route of administration is listed as (b) (4)	This statement can be improved to increase readability and comprehension by lay users.	We recommend revising this statement to read "For use in the nose only".

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for naloxone hydrochloride that Summit Biosciences Inc. submitted on March 24, 2023, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and naloxone hydrochloride		
Product Name	Narcan	Naloxone hydrochloride
Application Type and Number	NDA 016636	NDA 215487
Initial Approval Date	April 13, 1971	n/a
Active Ingredient	Naloxone hydrochloride	
Indication	Opioid overdose	
Route of Administration	Intravenous, intramuscular, subcutaneous	Intranasal
Dosage Form	Injection	Intranasal spray
Strength	0.02 mg/mL, 0.4 mg/mL, and 1 mg/mL	10 mg/ (b) (4) mL
Dose and Frequency	Dependent on indication and patient specific variables	Administer a single spray (10 mg) to adult or pediatric patients into one nostril. Seek emergency medical assistance as soon as possible after administering the first dose. If the desired response is not obtained after 2 or 3 minutes, administer a second dose using a new nasal spray device in alternate nostril. Do not administer more than 2 sprays per day.
How Supplied	Multiple-dose vials, ampules, single dose luer lock prefilled syringes	Unit dose nasal spray device in blister packaging, 2 blister packages per carton.
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 light. Store in carton until contents have been used.	Store below 77°F (25°C). Excursions permitted up to 104°F (40°C). Do not freeze or expose to excessive heat above 104°F (40°C). Protect from light. (b) (4) If this happens, the device will not spray. (b) (4)

		(b) (4)
Container Closure	Multiple-dose vials, ampules, single dose luer lock prefilled syringes	(b) (4) Intranasal Device

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 5, 2023, we searched for previous DMEPA reviews relevant to this current review using the term naloxone. Our search identified 21 previous reviews^{c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t,u,v,w} and we

^c Schlick J. Human Factors, Label, and Labeling Review for Nazque*** (NDA 205678). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 26. OSE RCM No.: 2015-1377 and 2015-1384.

^d Shah M. Human Factors, Label, and Labeling Review for Narcan (NDA 208411). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 3. OSE RCM No.: 2015-1531 and 2015-1532.

^e Shah M. Label and Labeling Review Memo for Narcan (NDA 208411). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 25. OSE RCM No.: 2015-1532.

^f Shah M. Label and Labeling Review for Narcan (NDA 208411/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 7. OSE RCM No.: 2016-905.

^g Shah M. Label and Labeling Review Memo for Narcan (NDA 208411/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 4. OSE RCM No.: 2016-905.

^h Shah M. Label and Labeling Review Memo for Narcan (NDA 208411/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 13. OSE RCM No.: 2016-905.

ⁱ Schlick J. Label and Labeling and Human Factors Results Review for Nazadone*** (NDA 208969). Silver Springs (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 17. OSE RCM No.: 2016-963 and 2016-964.

^j Johnson C. Label and Labeling Review for Narcan (NDA 208411/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 5. OSE RCM No.: 2018-1441.

^k Johnson C. Label and Labeling Review Memo for Narcan (NDA 208411/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 19. OSE RCM No.: 2018-1441-1.

^l Johnson C. Label and Labeling Review Memo for Narcan (NDA 208411/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 5. OSE RCM No.: 2019-902.

^m Johnson C. Labeling Review for naloxone hydrochloride (NDA 212045). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 5. OSE RCM No.: 2019-943.

ⁿ Farshneshani Z. Human Factors Study Report and Labels and Labeling Review for naloxone hydrochloride (NDA 212045). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 1. OSE RCM No.: 2019-944 and 2019-943.

^o Kumar N. Label and Labeling Review Memo for naloxone hydrochloride (NDA 212045). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 1. OSE RCM No.: 2019-943-1.

^p Birkemeier D. Label and Labeling Review for naloxone hydrochloride (NDA 212045/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 11. TTT No.: 2022-10.

^q Birkemeier D. Label and Labeling Review Memo for naloxone hydrochloride (NDA 212045/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 14. TTT No.: 2022-10-1.

^r Birkemeier D. Label and Labeling Review Memo for naloxone hydrochloride (NDA 212045/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 28. TTT No.: 2022-10-2.

^s 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 No.: 2022-1312 and 2022-1315.

^t Birkemeier D. Label and Labeling Review Memo for naloxone hydrochloride (NDA 208969). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 FEB 22. TTT No.: 2022-1315-1.

^u Shah M. Human Factors Study Report and Label and Labeling Review for Narcan (NDA 208411/S-006). Silver Spring (MD): FDA, OSE, CDER, DMEPA 2 (US); 2023 MAR 9. OSE RCM No.: 2022-2688 and 2022-2721.

^v Shah M. Label and Labeling Review Memo for Narcan (NDA 208411/S-006). Silver Spring (MD): FDA, OSE, CDER, DMEPA 2 (US); 2023 MAR 15. OSE RCM No.: 2022-2688-1.

^w Shah M. Label and Labeling Review Memo for Narcan (NDA 208411/S-006). Silver Spring (MD): FDA, OSE, CDER, DMEPA 2 (US); 2023 MAR 28. OSE RCM No.: 2022-2688-2.

considered our previous recommendations to see if they are applicable for this current review.

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,^x along with postmarket medication error data, we reviewed the following naloxone hydrochloride labels and labeling submitted by Summit Biosciences Inc. on March 24, 2023.

- Container labels
- Outer foil labeling
- Carton labeling
- Quick start guide (QSG)
- Instructions for use (IFU)
- Prescribing Information (PI) (Image not shown) available from <\\CDSESUB1\EVSPROD\nda215487\0001\m1\us\annotated-draft-labeling-text.pdf>

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^x Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DAMON A BIRKEMEIER
09/22/2023 03:19:55 PM

VALERIE S VAUGHAN
09/22/2023 03:24:57 PM

MEMORANDUM

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

DATE: 8/30/2023

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 on-site inspections**

RE: NDA 215487

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

Rationale

Novum, Las Vegas: The Office of Regulatory Affairs (ORA) conducted an inspection for the site in (b) (4). The inspection was conducted under the following submissions: (b) (4)

OSIS concluded that data from the reviewed studies were reliable.

(b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4). The RRA was conducted under the following submissions: (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	Novum Pharmaceutical Research Services, Inc.	3760 Pecos McLeod, Las Vegas, NV
Analytical	(b) (4)	

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/s/

ADANMA S OJI
08/30/2023 02:05:16 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

Division of Pediatrics and Maternal Health Review

Date: August 18, 2023 **Date of Consult Request:** May 15, 2023

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH

To: Lynne P. Yao, M.D., Division Director, DPMH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

NDA Number: 215487

Drug: Naloxone nasal spray

Applicant: Summit Biosciences Inc.

Indication: Indicated for the emergency treatment of known or suspected opioid (b) (4) overdose, as manifested by respiratory and/or central nervous system depression. Naloxone nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present. Naloxone nasal spray is not a substitute for emergency medical care.

Subject: Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR).

Materials Reviewed

- Applicant's original submission of March 24, 2023.

- Division’s Consult request of May 15, 2023, DARRTS Reference ID: 5174226.
- Opvee (nalmefene) labeling review by Christos Mastroyannis, M.D., in DARRTS and dated May 10, 2023, Reference ID: 5170486.¹
- Narcan (naloxone hydrochloride) Nasal Spray labeling review by Suchitra M. Balakrishnan, M.D., Ph.D., in DARRTS and dated October 26, 2015, Reference ID: 3834852.¹

INTRODUCTION

On March 24, 2023, the applicant, Summit Biosciences Inc., submitted an original NDA 215487 for Naloxone nasal spray (NS), 10 mg, under the 505(b)(2) pathway, for the emergency treatment of known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression. Naloxone nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present. Naloxone nasal spray is not a substitute for emergency medical care.

The clinical development program for Naloxone Hydrochloride NS, 10 mg, relies on the FDA's previous findings of safety and effectiveness for the drug relied upon Narcan (naloxone hydrochloride injection, USP, NDA 016636). Narcan was first approved by the Food and Drug Administration in 1971 and is indicated for use in adults and pediatric patients of all ages. Narcan may be administered by the intravenous (IV), intramuscular (IM) or subcutaneous (SC) routes in adults, children, and neonates to reverse the effects of opiates. This current application cross-references to nonclinical information from Narcan (NDA 016636). Because the dosage of 10 mg/spray is a new (higher strength) dosage than had been previously approved for naloxone intranasal administration,² repeat-dose intranasal toxicology bridging studies to assess local toxicity were completed in the rat for 28 days and in the dog for 14 days to support clinical development. The proposed labeling is in PLR and PLLR format. DAAP has requested DPMH to ensure that the labeling complies with the PLLR content and format.

BACKGROUND

The opioid epidemic continues in the United States, with over 550,000 opioid overdose deaths since 1999 (CDC–2021)^{3,4}. Recent studies provide evidence that individuals who survive a nonfatal opioid overdose are at higher risk of a subsequent overdose both within 30 days and over the next 12 months following the initial event. For example, in a retrospective study of over 4100 patients who survived an overdose, ~15% of patients had a repeat overdose, with 29% occurring within the first 30 days.⁵ Respiratory depression is responsible for opioid-induced deaths as well as the short- and long-term morbidities linked to a non-fatal overdose including brain injuries produced by hypoxia

¹ DPMH did not rely on data in the Opvee (nalmefene) NDA 217470 or the Agency’s findings of safety and effectiveness for the NDA to support labeling sections of this Naloxone nasal spray NDA. Rather, the cross-reference to the Opvee NDA consult is included to avoid duplicating background information relevant to this class of products.

² Other approved naloxone hydrochloride nasal sprays includes Kloxxado NDA 212045 that delivers 8 mg/spray of naloxone hydrochloride to one nostril and Narcan NS that delivers 4 mg/spray of naloxone hydrochloride to one nostril.

³ Center of Disease Control. Data tables for NCHS Data Brief, no 428. Hyattsville, MD: National Center for Health Statistics. 2021:1-3.

⁴ Center for Disease Control. Health Alert Network. Increase in Fatal Drug Overdose Across the United States Driven by Synthetic Opioids Before and During the Covid 19 Pandemic. December 2020.

⁵ Suffoletto B., Ziegler A. Risk and protective factors for repeated overdose after opioid overdose survival. Drug and Alcohol Dependence. 2020;209:107890.

and in more severe cases, anoxia.^{6,7}

Narcan (Naloxone) Nasal Spray Drug Characteristics⁸

Half Life	3.1 ±0.5 hours in neonates/ 1.33 hours adults
Molecular Weight	327.27 gr/mol
Protein bound	45%
Oral Bioavailability	<3%
Bioavailability of nasal spray	47% (24-66%)
Administration	Intranasally
Dosage	One spray delivered by intranasal administration. Do not administer more than 2 sprays/day
Treatment duration	• Seek medical care immediately after use. Since the duration of action of most opioids exceeds that of naloxone hydrochloride and the suspected opioid overdose may occur outside of supervised medical settings, seek immediate emergency medical assistance, keep the patient under continued surveillance until emergency personnel arrive, and administer a second dose of Naloxone Nasal Spray, as necessary. Always seek emergency medical assistance in the event of a suspected, potentially life-threatening opioid emergency after administration of the first dose of Naloxone Nasal Spray. • An additional dose of Naloxone Nasal Spray may be required before emergency medical assistance becomes available.
Mechanism of action	Naloxone is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites

REVIEW

Pregnancy

Non-clinical Data

This application cross-references to nonclinical information from Narcan (NDA 016636). In reproductive studies conducted in mice and rats treated with naloxone hydrochloride at doses equivalent to 2-times and 4-times, respectively, a human dose of 20 mg/day (2 sprays of naloxone nasal spray) based on body surface area, there were no embryotoxic or teratogenic effects observed due to naloxone hydrochloride.

Clinical Data

No new information exists other than what is included in Narcan's labeling. Available data from retrospective cohort studies on naloxone use in pregnant women have not identified a drug-

⁶ Skolnick P. Treatment of overdose in the synthetic opioid era. Opiant Pharmaceuticals, 233 Wilshire Blvd., Suite 280, Santa Monica, CA 90401, United States of America.

⁷ Boyer EW. Management of Opioid Analgesic Overdose. N Engl J Med Drug Therapy. 2012;367:146-55.

⁸ Narcan approved labeling of March 27, 2023.

associated risk of major birth defects or miscarriage or other adverse maternal or fetal outcomes. Currently approved naloxone labeling notes that naloxone crosses the placenta, and there is the potential for neonatal and maternal opioid withdrawal.

The American College of Obstetrics & Gynecology⁹ notes the following about naloxone, an opioid antagonist, and opioid withdrawal in pregnant women: “Although induced withdrawal may possibly contribute to fetal stress, naloxone should be used in pregnant women in the case of maternal overdose in order to save the woman’s life.”

Reviewer Comment

Although induced opioid withdrawal may contribute to fetal stress, naloxone should be used in pregnant women with known or suspected opioid overdose to save the woman’s life. Additionally, the optimal method for fetal assessment during patient stabilization is unknown, and there are no data to support an approved protocol for fetal assessment and monitoring for opioid withdrawal. Therefore, DPMH does not recommend language about monitoring the fetus for potential naloxone-precipitating opioid withdrawal. Because naloxone is used in life-threatening situations, it should not be withheld in pregnant women due to lack of data to support monitoring for fetal opioid withdrawal.

Summary

Available data on naloxone use in pregnant women have not identified a drug-associated risk of major birth defects or miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, no embryotoxic effects on embryo-fetal development were observed in mice and rats treated with naloxone at exposures up to 4 times the exposure at human nasal dose of 20 mg/day. Life-sustaining therapy for the pregnant woman should not be withheld due to lack of existing data for potential effects of naloxone on the fetus.

Lactation

Non-Clinical Data

The applicant did not conduct any non-clinical studies, but cross-references to nonclinical information from Narcan (NDA 016636). There is no information available on the presence of naloxone in human or animal milk.

Clinical Review of Data

There is no information regarding the presence of naloxone in human milk, or the effects of naloxone on the breastfed infant or on milk production. Naloxone is minimally orally bioavailable. Published studies in lactating women have shown that naloxone does not affect prolactin or oxytocin hormone levels.^{10,11}

Summary

There are no available human data on the presence of naloxone in human milk, the effects on the breastfed infant, or the effects on milk production. There is reasonable expectation that breast-feeding an infant will not take place when a mother has experienced a life-threatening situation such as opioid overdose-induced respiratory and CNS depression.

DPMH has previously not recommended inclusion of the standard risk/benefit statement for naloxone products since the indication is for emergent treatment of opioid overdose and a similar approach is also recommended for

⁹ Committee on Obstetric Practice. Opioid Use and Opioid Use Disorder in Pregnancy. ACOG Number 711. August 2017.

¹⁰ Cholst IN, Wardlaw SL, Newman CB, Frantz AG. Prolactin response to breast stimulation in lactating women is not mediated by endogenous opioids. American journal of obstetrics and gynecology. 1984;150(5 Pt 1):558-61.

¹¹ Johnson MR, Andrews MA, Seckl JR, Lightman SL. Effect of naloxone on neurohypophyseal peptide responses to breast feeding and breast stimulation in man (humans). Clinical endocrinology. 1990;33(1):81-6.

this product.

Females and Males of Reproductive Potential

Non-Clinical Data

Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study. Male rats were treated with 2 or 10 mg/kg naloxone for 60 days prior to mating. Female rats were treated for 14-days prior to mating and throughout gestation with the same doses of naloxone [up to 4.8-times a human dose of 20 mg/day (two Naloxone Nasal Sprays) based on body surface area comparison]. There was no adverse effect on fertility.

Clinical Data

No relevant published information was identified by either the applicant or this reviewer for naloxone use in patients of reproductive potential.

Summary

Naloxone does not have any reported effects on fertility, and (based on animal studies) is not teratogenic. No new safety information was identified regarding the use of naloxone in females and males of reproductive potential. Therefore, there is no need for pregnancy testing or contraception recommendations in labeling. Labeling subsection 8.3 Females and Males of Reproductive Potential will be omitted.

CONCLUSION

Animal reproduction studies with naloxone have not demonstrated any evidence of embryo-feto-toxicity. The prolonged clinical use of various formulations of naloxone over decades and the available data from published retrospective cohort studies on naloxone use in pregnant women have not identified a drug-associated risk of major birth defects or miscarriage, or other adverse maternal or fetal outcomes. Currently approved naloxone labeling notes that naloxone crosses the placenta, and there is the potential for neonatal and maternal opioid withdrawal. Although induced opioid withdrawal may contribute to fetal stress, naloxone should be used in pregnant women with known or suspected opioid overdose to save the woman's life. Life-sustaining therapy for the pregnant woman should not be withheld due to lack of data on the potential effects of naloxone on the fetus. There are no new data or safety information to be included in this labeling. DPMH has made some editorial changes to better align with the current PLLR practices. These changes are underlined to better be identified, while other existing or proposed language has been strikethrough.

There is no data on the presence of naloxone in human milk, the effects of on the breastfed child, or the effects on milk production.

There are no data on fertility effects of naloxone in patients of reproductive potential.

DPMH does not recommend a Post Marketing Requirement (PMR) for a descriptive pregnancy safety study or a clinical lactation milk-only study to collect safety data because there is no new safety information that DPMH has identified that would warrant a PMR at this time. In addition, such studies will be difficult to conduct in this patient population. The information collected will be highly confounded with other medications used in the critical care setting. This is one time use of the naloxone nasal spray in a life-threatening situation.

DPMH LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of Naloxone nasal spray 10 mg labeling for compliance with the PLLR (see below). Revised or new labeling language is formatted with underline, deletions with ~~strikethrough~~. DPMH refers to the final NDA action for final labeling.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Life-sustaining therapy for opioid overdose should not be withheld (see Clinical Considerations). Available data from retrospective cohort studies on naloxone use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. (b) (4)

(b) (4)

In animal reproduction studies, no embryotoxic or teratogenic effects were observed in mice and rats administered naloxone hydrochloride during organogenesis at doses equivalent to 2-times and 4-times, respectively, a human dose of 20 mg/day (two sprays of naloxone) (see Data).

The (b) (4) background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

An opioid overdose is a medical emergency and can be fatal for the pregnant woman and fetus if left untreated. Treatment with TRADENAME for opioid overdose should not be withheld because of potential concerns regarding the effects of TRADENAME on the fetus.

(b) (4)

Data

Animal Data

Naloxone hydrochloride was administered to pregnant mice and rats at subcutaneous doses of up to 10 mg/kg/day (equivalent to up to 4.8-times a human dose of 20 mg (two naloxone Nasal Sprays)). These studies demonstrated no evidence of teratogenic effects or embryotoxicity with naloxone hydrochloride.

8.2 Lactation

Risk Summary

There is no information regarding the presence of naloxone in human or animal milk, the effects of (b) (4) on the breastfed infant, or the effects of the drug on milk production. (b) (4) -
(b) (4) . Published
studies in lactating women have shown that naloxone does not affect prolactin or oxytocin hormone levels. Naloxone is minimally orally bioavailable. (b) (4) -
(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
08/18/2023 09:50:44 AM

TAMARA N JOHNSON
08/18/2023 01:30:10 PM

LYNNE P YAO
08/18/2023 02:08:32 PM

HUMAN FACTORS VALIDATION STUDY REPORT 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)

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

Date of This Review:	August 04, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215487
Product Type:	Combination Product
Product Name, Dosage Form, and Strength:	naloxone hydrochloride nasal spray, 10 mg
Device Constituent:	Nasal Spray
Rx or OTC:	Rx
Applicant/Sponsor Name:	Summit Biosciences Inc.
Submission Date:	March 24, 2023
TTT ID #:	2023-4168
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results report submitted under NDA 215487 for naloxone hydrochloride nasal spray, 10 mg.

1.1 PRODUCT DESCRIPTION

Table 1. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Opioid antagonist
Active Ingredient (Drug or Biologic)	Naloxone hydrochloride
Indication	Opioid overdose
Route of Administration	intranasal
Dosage Form	nasal spray
Strength	10 mg (b) (4) mL
Dose and Frequency	Administer a single spray (10 mg) to adult or pediatric patients into one nostril. Seek emergency medical assistance as soon as possible after administering the first dose. If the desired response is not obtained after 2 or 3 minutes, administer a second dose using a new nasal spray device in alternate nostril. Do not administer more than 2 sprays per day.
How Supplied	Unit dose nasal spray device in blister packaging, 2 blister packages per carton.
Storage	Store below 77°F (25°C). Excursions permitted up to 104°F (40°C). Do not freeze or expose to excessive heat above 104°F (40°C). Protect from light. If this happens, the device will not spray. (b) (4)

Container Closure/Device Constituent	 Product Carton Individual Nasal Device In Blister Pack (sealed and opened)
	(b) (4) Intranasal Device
Intended Users	Lay users (adults and adolescents' users), first responders
Intended Use Environment	Public, domestic, and emergency environments

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On October 12, 2018, the Applicant submitted a Type B Meeting request under IND 141634 to discuss the development program for Naloxone Hydrochloride Nasal Spray, 10 mg. We granted the meeting as a face-to-face meeting, and on February 07, 2019 we had the meeting with the Applicant. In the meeting minutes dated March 07, 2019, we provided HF comments recommending the Applicant submit a comprehensive URR, CA, and justification for not submitting an HF validation study.¹

¹ Walker, D. Type 2 Meeting Minutes for Naloxone Nasal Spray (IND 141634). Silver Spring (MD): FDA, CDER, OND, DAAP (US); 2019 MAR 07. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804e252a>

- On July 10, 2020, the Applicant submitted a Type C Meeting request under IND 142850 to discuss the chemistry/manufacturing/controls (CMC), nonclinical and clinical information necessary for the continued development of Summit's Naloxone Hydrochloride Nasal Spray, 10 mg via the 505(b)(2) New Drug Application (NDA) pathway. We granted the meeting as a written response. The Applicant's Meeting Package included their URRRA, CA and justification for not submitting an HF validation study and they asked if we concurred that they do not need to include HF validation study results in their NDA submission. In the information request dated September 29, 2020, we informed the Applicant that submitting the aforementioned information as part of a meeting request is not the appropriate mechanism to obtain the Agency's feedback. We recommended the Applicant resubmitted their URRRA, CA and justification to the IND.²
- On October 08, 2020, the Applicant submitted a URRRA and CA under IND 142850 for Naloxone Hydrochloride Nasal Spray, 10 mg, to determine whether the Applicant needs to submit HF validation study results as part of their marketing application.
- On October 27, 2020, in the final written response letter, we responded to the Applicant's question asking if we concurred that they do not need to include HF validation study results in their NDA submission by indicating that their URRRA/CA submission was currently under review and we will notify them if we concur with their determination.³
- On August 30, 2021, We reviewed the Applicant's URRRA, CA and justification dated October 08, 2020, and provided the following recommendations:

"Based on our evaluation of your comparative analyses and use related risk analysis, we have determined that you will be required to submit HF validation study data to support your marketing application to the Agency for review. Based on your November 12, 2020, email response to the Agency, you have specifically noted that you have concerns with using Narcan® Nasal Spray as the comparator in the HF comparative analyses.

[REDACTED] (b) (4)

[REDACTED]

[REDACTED], we disagree with your conclusion from your submission. You should submit your HF validation study data for the

² Joshi, R. Information Request Type 2 Meeting Minutes for Naloxone Nasal Spray (IND 142850). Silver Spring (MD): FDA, CDER, OND, DAAP (US); 2020 SEP 29. Available from:

<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8059bda5>

³ Joshi, R. Final Type 2 Written Response for Naloxone Nasal Spray (IND142850). Silver Spring (MD): FDA, CDER, OND, DAAP (US); 2020 OCT 27. Available from:

<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805a4bde>

Agency to review to support your marketing application for your naloxone nasal spray.

In addition, we identified a labeling concern with the proposed blister pack additional “peel here” indicator which may lead to confusion resulting in a delay of therapy. Specifically, we find that the location of your “peel here” indicator can be improved to decrease the risk misinterpretation. Therefore, we recommend you consider increasing the prominence or revise your packaging so that the “peel here” indicator for the QSG is adequately differentiated from the “peel here” indicator to open the blister package. The acceptability of your revision will be a review issue once you submit your NDA.”⁴

- On March 24, 2023, the Applicant submitted a new drug application (NDA) for Naloxone Hydrochloride Nasal Spray, 10 mg under NDA 215487. This submission included HF validation study results report, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	Section 1.1
Background Information Previous HF Reviews (DMEPA)	A
Background Information on Human Factors Engineering (HFE) Process	B
Human Factors Validation Study Report	C
Information Requests Issued During the Review	D
Labels and Labeling	E

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface supports the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

⁴ Roosta N. Comparative Analyses Review for Naloxone Nasal Spray (IND 142850). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 AUG 30. RCM No.: 2020-2125.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	• 15 Adults participants. This group also included a mix of 8 individuals who are experienced using nasal spray products and 7 individuals who are naïve to them. • 15 Juvenile participants between the ages of 10 and 17 years old. This group also included a mix of 6 individuals who are experienced using nasal spray products and 9 individuals who are naïve to them. • 15 First responders (e.g., firefighter, paramedic, emergency medical technician, police officer, or ER nurse). This group also included a mix of 7 individuals who are experienced using nasal spray products and 8 individuals who are naïve to them.
Training	Study participants did not receive training.
Test Environment & Materials	The test room was setup to simulate a home or public environment. Accordingly, to simulate these conditions, the test room was set up where sound file was playing (ambient noise), with a table and chairs off to the side with a manikin lying on the ground. For lay bystanders, the product was in a bag on the ground, next to the unconscious person. First responders walked into the test room with the product blisters. Additionally, dependent upon the participant's assigned condition, the manikin was either an adult sized manikin or an infant/toddler sized manikin. The room environment included ambient sound simulating a public space or crowd played at a high level of ~75db.



Study Articles

The following materials were used for this study:



Carton (containing 2 blister packs and IFU)



Laptop for background sounds



Gloves (First responders only)



Adult sized manikin



Infant/toddler sized manikin

	 <i>Ancillary items (trash can, telephone, clock)</i>  <i>Pouch Holding Blisters (Lay responders only)</i>
Sequence of Study	Simulated use Debriefing of use errors/use difficulties/close calls Knowledge-based task questions Debriefing of errors Qualitative questions (post-use interview)

3 RESULTS AND ANALYSES

We have carefully reviewed each observed event, the applicant's URRAs, the participants' subjective feedback, the applicant's RCA, and the Applicant's comments and proposed mitigations below.

Table 4. Analysis of Use Errors, Use Difficulties and Close Calls and DMEPA's Recommendations

Information Supplied by Applicant		DMEPA's Findings and Recommendations				
Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis Participants ID: AL: General Population Adults, Ages 18 and Older; AD: General Population Adolescents, Ages 10-17; FR: First Responders (Police, EMT, Firefighter, Paramedic)						
Task: Position Person on Back <table border="1"> <tr> <td>Errors:</td> <td>Participant Type:</td> </tr> <tr> <td>UE (n=3)</td> <td>P22-Juvenile user, P32 and P45- First Responders</td> </tr> </table>		Errors:	Participant Type:	UE (n=3)	P22-Juvenile user, P32 and P45- First Responders	
Errors:	Participant Type:					
UE (n=3)	P22-Juvenile user, P32 and P45- First Responders					
Observed error(s): Participants did not place the patients on their back when the second dose was delivered.						
Risk associated with Task Errors (Per Applicant URRRA): if this task is omitted or performed incorrectly there is no harm.		We contacted the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) Medical Officer (MO) regarding the Applicant's statement. The DAAP MO indicated that there is no harm if this task is omitted or performed incorrectly. The purpose of this task is to optimize the absorption of the product through the nasal mucosa.				
Relevant RCA/Subjective Feedback/Observation: - One participant did not lay the person on their back before dosing because they did not see instruction to turn the person on their back in Step 9. The participant recommended adding to put the person on their back before giving the second dose. Another participant self-identified that they should have put the person on their back after reviewing the full IFU during the knowledge task question. The participant recommended including a picture of the person on their back and to include instruction to turn the person on their back in Step 9. - One participant stated they felt it was unclear in the Quick Start Guide (QSG) whether the person should be on their back during the second dose or not and felt it was safer to keep them in the recovery position. The participant recommended that the QSG explicitly state to turn the person on their back.						
Applicant Comment and Proposed Mitigations: none The Applicant stated, "A potential mitigation for these errors is to either include a reference to steps 2-6 in step 9 of the QSG or		Our review of the user interface and labels and labeling indicates that the IFU and QSG contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we did				

<i>include an instruction telling users to position the person on their back before completing the 2nd dose. However, due to the fact that these errors would not impact dosing and the task is not critical, mitigating these errors may not be necessary. If the changes are made to the QSG, it would not justify any further testing as the changes are small and would not impact users ability to be successful using the QSG."</i>	not identify areas of improvement and have no recommendations at this time.				
Task: Call 911: Put person into recovery position <table border="1" data-bbox="321 428 846 521"> <tr> <td>Errors:</td> <td>Participant Type:</td> </tr> <tr> <td>UE (n=2)</td> <td>P34 and P37-First Responders</td> </tr> </table> Observed error(s): Participants did not put the patient into the recovery position. Risk associated with Task Errors (Per Applicant URR): if this task is omitted or performed incorrectly there is risk of the person choking/harm to person or death. Relevant RCA/Subjective Feedback/Observation: • Instruction not prominent : participant stated that they did not notice the second part of step 9 when performing the procedure. To mitigate this issue, the participant recommended separating step 9 into two steps. • Forget: The participant stated that they forgot to turn the person on their side after giving the first dose but mentioned that it is clearly presented in the instructions. The participant offered no changes to the instructions to mitigate the error but did suggest having text on the side of the device to tell users to turn the person on their side.	Errors:	Participant Type:	UE (n=2)	P34 and P37-First Responders	
Errors:	Participant Type:				
UE (n=2)	P34 and P37-First Responders				
Applicant Comment and Proposed Mitigations: none The Applicant stated indicated that though not putting the person into a recovery position could result in harm, it would not have as the person dosing was monitoring the person and could have responded to any issues that arise.	Our review of the IFU indicates that, step 9 includes instructions and figure to put person on their side. However, based on subjective feedback (participants did not see the instruction, one participant suggested separating step 9 into two steps), and our overall assessment, we find that the step 9 can be improved to be more prominent. 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.				
Task: Give Second Dose: If no response, Give a 2nd dose in the other nostril <table border="1" data-bbox="321 1349 879 1409"> <tr> <td>Errors:</td> <td>Participant Type:</td> </tr> <tr> <td>UE (n=2)</td> <td>P12- Adult User, P20- Juvenile User</td> </tr> </table>	Errors:	Participant Type:	UE (n=2)	P12- Adult User, P20- Juvenile User	
Errors:	Participant Type:				
UE (n=2)	P12- Adult User, P20- Juvenile User				

Observed error(s): Participants gave the second dose in the same nostril as the first dose.	
Risk associated with Task Errors (Per Applicant URRRA): if this task is omitted or performed incorrectly there is risk of • Reduced medication efficacy • Reduced symptom relief.	
Relevant RCA/Subjective Feedback/Observation: • The participant did not give the dose into the other nostril because he did not notice to dose in other nostril because he was more focused on Step 8 (monitoring the person for 2 minutes). The participant recommended changing the callout in Step 9 to a different color but mentioned that the current callout does stand out. • The participant did not notice the information in the instructions to dose in separate nostrils as she was reading too fast. The participant attributed this error to herself and did not recommend any changes to the instructions.	
Applicant Comment and Proposed Mitigations: none The Applicant stated, "These errors are not attributed to the product design or the design of the instructional materials. There is no clear mitigation to make the information more salient than it already is."	Our review of the user interface and labels and labeling indicates that the IFU and QSG contains instructions and/or images to support this task. Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.

3.2 LABELS AND LABELING

Table A below includes the identified medication error issues with the submitted instructions for use (IFU) based on the HF study results, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. Additionally, we note that the DMEPA 1 primary review team will evaluate product specific labels and labeling under separate cover.

Table A: Identified Issues and Recommendations for Summit Biosciences Inc. (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The instructions in Step 9 to put the person on their side is not prominent.	Per the URRRA, if the user does not put person on their side, there is risk of the person choking/harm to person or death. The HF validation study results identified subjective feedback that indicated that that some participants did not see the instruction.	Consider revising step 9 to make the instructions to put the person on their side more prominent. For example you may consider making the statement “ return the person to the recovery position” as a separate step.

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified an additional risk mitigation to address the use errors. Above, we have provided a recommendation in Table A for the Applicant. We ask that the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) convey Table A in its entirety to the Applicant. This change can be implemented without submitting additional HF validation testing data for Agency review.

4.1 RECOMMENDATIONS FOR THE SUMMIT BIOSCIENCES INC.

Our evaluation of your human factors (HF) validation study indicates that there is an additional mitigation that can be implemented to address use errors that occurred with critical task. We provide a recommendation in Table A, and we recommend that you implement this recommendation and submit the revised label and labeling for our review. We have determined that in this instance, you may implement this revision without submitting additional human factors validation data for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. BACKGROUND INFORMATION

A.1 PREVIOUS HF REVIEWS

A.1.1 Methods

On July 04, 2023, we searched the L:drive and AIMS using the terms, IND 142850, IND 141634 , NDA 215487, to identify reviews previously performed by DMEPA.

A.1.2 Results

Our search identified one previous review⁴, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX B. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF study results report. See Appendix C.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\nda215487\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\opiod-overdose\5354-other-stud-rep\iaa-2134\report-body.pdf>

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁵ along with postmarket medication error data, we reviewed the following Opvee labels and labeling submitted by Summit Biosciences Inc. on March 24, 2023.

- Container labels
- Carton Labeling
- Quick Start Guide (QSG)
- Instructions for use (IFU)

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Prescribing information, Instructions for Use (Image not shown), available from EDR via: <\\CDSESUB1\EVSPROD\nda215487\0001\m1\us\annotated-draft-labeling-text.pdf>

E.2 Label and Labeling Images



4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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