

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212045Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 23, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 212045
Product Name and Strength:	naloxone hydrochloride nasal spray, 8 mg
Applicant/Sponsor Name:	Hikma Pharmaceuticals USA INC (Hikma)
OSE RCM #:	2019-943
DMEPA Safety Evaluator:	Neha Kumar, PharmD
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 12, 2021 for naloxone hydrochloride nasal spray 8 mg. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels and carton labeling for naloxone hydrochloride nasal spray 8 mg (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.^a

2 CONCLUSION

In response to our recommendations to add the lot number and product identifier to the labeling, we note the Applicant indicated the location of the lot number on the container label, carton labeling, and blister labeling and provided the designated area where the product identifier will be printed on the carton labeling. Additionally, we note the Applicant confirmed

^a Farshneshani F. Human Factors Study Report and Labels and Labeling Review for naloxone hydrochloride nasal spray 8 mg (NDA 212045). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 01. RCM No.: 2019-944 and 2019-943.

the expiration date format is MMMYYYY. Thus, we note they implemented all of our recommendations and we have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 12, 2021

Available from: \\CDSESUB1\evsprod\nda212045\0036\m1\us\questions-responses-to-fda-letter-20210407.pdf

Container label



Carton labeling



Blister labeling

(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/

NEHA KUMAR
04/23/2021 03:23:38 PM

EBONY A WHALEY
04/25/2021 08:29:21 PM

LOLITA G WHITE
04/26/2021 09:39:54 AM

Date	4/27/2021								
To:	Anika Lalmansingh								
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	DAAAP						
From	Michaela Schulman OPEQ/OHT3/DHT3C								
Through (Team)	Rumi Young, Acting Assistant Director, Injection Team OPEQ/OHT3/DHT3C								
Through (Division) *Optional	CPT Alan Stevens, Acting Director OPEQ/OHT3/DHT3C								
Subject	NDA 212045 , Naloxone ICC1900405, ICC1900397, ICC2000966 ICC1900397: 00010719 (Facilities), 00010716 (Premarket) – CR issued 2/28/2020 ICC2000966: 00039030 (Facilities), 00038754 (Premarket)								
Recommendation	<u>Previous Submission</u> Original Filing Recommendation Date: 6/4/2019 ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. A PAI inspection is recommended. Original Mid-Cycle Recommendation Date: 10/4/2019 ☒ CDRH has additional Information Requests, Section 11. Original Final Recommendation Date: 12/16/2019 ☒ Device Constituent Parts of the Combination Product are Not Approvable The submission does NOT include adequate information. CDRH recommends that the applicant be issued a CR letter with outstanding deficiencies related to the device constituent (See CR deficiencies in Section 12.1). In addition, a preapproval inspection of the following firm is recommended: <table border="1"> <tr> <td>Firm Name:</td><td>West-Ward Columbus Inc.</td></tr> <tr> <td>Address:</td><td>1809 Wilson Road (b) (4), Columbus, Ohio, USA</td></tr> <tr> <td>FEI:</td><td>1510690 (DUNS #058839929)</td></tr> </table> <u>Resubmission Final Recommendation Date: 3/29/2021</u> ☒ 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 The facilities were inspected 4/16/2019. No further PAI is necessary. *Note: All comments from the re-submission review are highlighted in blue.			Firm Name:	West-Ward Columbus Inc.	Address:	1809 Wilson Road (b) (4), Columbus, Ohio, USA	FEI:	1510690 (DUNS #058839929)
Firm Name:	West-Ward Columbus Inc.								
Address:	1809 Wilson Road (b) (4), Columbus, Ohio, USA								
FEI:	1510690 (DUNS #058839929)								

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 212045
Sponsor	Insys Development Company, Inc.
Drug/Biologic	Naloxone
Indications for Use	Emergency Treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system. Immediate administration as emergency therapy in setting where opioids may be present.
Device Constituent	Nasal Spray
Related Files	N/A

Review Team		
Lead Device Reviewer	Rumi Young - (Filing Recommendations; including inspection recommendation) Matthew Ondeck - (Midcycle, Filing Review) – CR Deficiencies Issued Michaela Schulman – (Resubmission, Facilities) See ORIGINAL RECOMMENDATION for the CR Deficiencies and the Sponsor's Resubmission Response	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
None	None	None

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	N/A
Interim Due Dates	Meeting/Due Date
Filing	N/A
74-Day Letter	N/A
Mid-Cycle	
Facilities Review Due	2/26/2021
Device Review Due	3/29/2021
Primary Reviews Due	

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2. PURPOSE/BACKGROUND

2.1. Scope

Insys Development Company, Inc. is requesting approval of Naloxone nasal spray. The device constituent of the combination product is a nasal spray device. CDER has requested a consult of the nasal spray device from a device constituent standpoint and from a device facilities standpoint. The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product.

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

2.2. Prior Interactions

There were device related type B comments (under IND 134954) issued in 2018 to the Sponsor. The CDRH reviewer was Matthew Ondeck.

N/A

2.3. Indications for Use

Combination Product	Indications for Use
Naloxone	Emergency Treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system. Immediate administration as emergency therapy in setting where opioids may be present.
Nasal Spray	Delivery of the Drug Product

2.4. Materials Reviewed

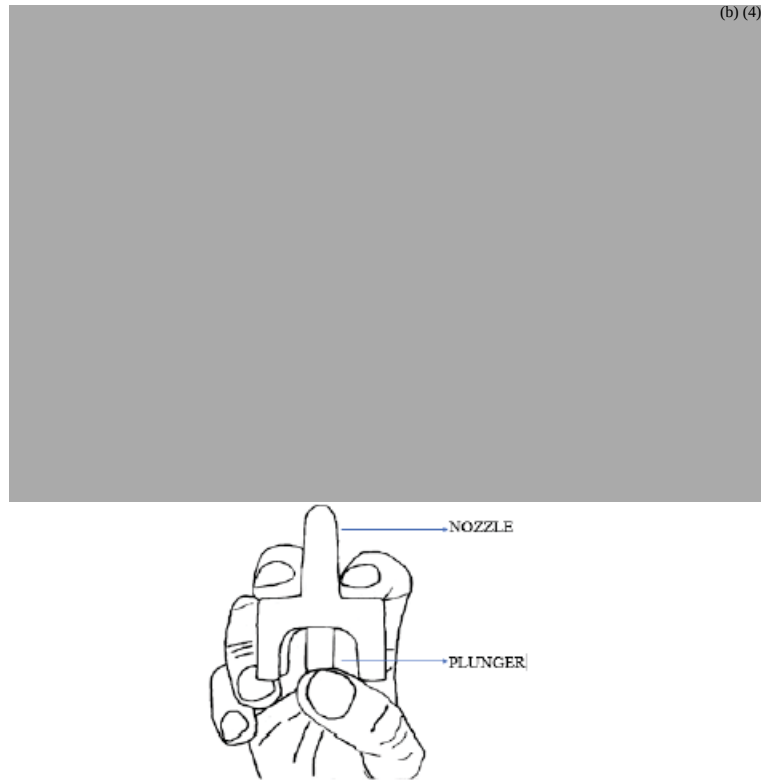
Materials Reviewed	
Document Name	Location
container-closure-system	Seq0000.3.2.P.7
ifu-proposed	Seq0000.1
questions-responses	Seq0016.1
questions-responses-crl-recd-02282020.pdf	Seq0000.1.11.4

3. DEVICE DESCRIPTION

3.1. Device Description

The sponsor is proposing a nasal spray for the emergency delivery of ~100 uL of (8 mg) naloxone hydrochloride. It is packaged in a blister (b) (4). The drug is stored in a glass primary container and rubber stopper.

The following information was obtained from Seq000.3.2.P.7: doc: container-closure-system.



When the user pushes the container holder into the actuator it causes the cannula to penetrate the stopper. The spray pin forces the stopper down to the bottom of the container. The liquid then moves from the container through the cannula into the actuator generating a spray through the end orifice.

The sponsor describes the actuation/device as:

The container holder/vial holder is connected to the actuator (b) (4). After applying a pre-determined force to the bottom of the container holder, the (b) (4) container holder, bearing the filled and sealed container moves upwards, allowing the cannula to penetrate the stopper (plunger). While continuing the actuation, the spray pin forces the plunger down to the bottom of the container. The liquid formulation escapes during this action through the cannula up into the actuator and leaves the orifice of the device, generating a spray. The resulting high-speed actuation makes the spray performance independent of the user.

No priming is necessary for the nasal unit dose delivery system. The target fill volume of the via is (b) (4) μ L. Upon actuation, devices deliver about 100 μ L of the product solution to the nasal cavity. One spray corresponds to one dose (8 mg) of Naloxone Hydrochloride administered intranasally.

For commercial use, the labeled unit dose spray devices are packaged in individually-sealed transparent blister packages (b) (4). The blister cavity is sealed (b) (4), so it has a peel off side. Two individual blisters are placed in the carton.

Reviewer Note:

The sponsor states the following:

*Please note that during development, two formulations, both delivering 8 mg of Naloxone Hydrochloride per spray, were considered for emergency treatment of known or suspected opioid overdose: one of them containing 20% of alcohol and another, (b) (4) % of alcohol. **Only the 20% alcohol formulation is proposed for approval.** Nevertheless,*

because most of the development work and pivotal clinical studies were done with both formulations, batch analysis data presented in this application include both formulations. Moreover, the compositions of the formulations containing 20% and (b) (4)% are similar, with the major differences being the concentrations of alcohol (20% and (b) (4)%), and purified water (b) (4) (b) (4)). Therefore, the data generated for the (b) (4)% alcohol formulation serves as a supporting information for the formulation containing 20% alcohol.

This will be noted when performance testing is reviewed. The sponsor will need to ensure that adequate bridging is provided to demonstrate that testing with the (b) (4)% product, will support approval of the 20% product.

The sponsor provides the individual components with the materials and manufacturers below:

Table 1: Naloxone Nasal Spray - Description of Each Packaging Component

Packaging Use	Part Description	Material Description	Manufacturer and DMF Reference (if applicable)
Primary container	Vial	(b) (4)	(b) (4)
Primary closure	Stopper (plunger)		
Spray	Actuator		
	Vial Holder		
	Integrated spray pin		
	Spray insert		
	(b) (4)		

The sponsor provides the Letter of Authorization to the (b) (4) in document (b) (4) and has stated that the device components and materials are unchanged from the clinical to the to be marketed devices.

Reviewer Note:

The (b) (4) device provided under DMF (b) (4) has been approved under NDA 208411 for emergency use Narcan.

3.2. Steps for Using the Device

A review of the steps needed to use the device constituent to administer the drug product properly is provided in the review of the instructions for use. The proposed instructions for use document is provided in: ifu-proposed in Seq000.1. The steps associated with use are the following:

- Lay user on their back
- Remove product from carton
- Hold Nasal Spray
- Tilt the person's head back and insert nozzle into nostril
- Press the plunger and administer dose
- Remove from nostril
- Get emergency help

3.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION	
The Device Description is Adequate.	

4. FILING REVIEW

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

4.1. 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		
	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

The sponsor provided all information needed to file.

4.2. Facilities Information (Prior to 9/20/2019)

The Sponsor provides information regarding the associated manufacturers in Seq0000.3.2.P.3; doc: naloxone-function-responsibilities:

Reviewer Note – Update 10/1/2019

On 10/1/2019, CDER/OPQ reviewer Venkateswara Pavuluri, sent the following email: *Per the response to a CMC request for information received on Sept. 20th, current NDA sponsor (Hikma) has added a new drug product manufacturing facility (West-Ward Columbus Inc. FEI 1510690) while withdrawing originally proposed facility (Insys). Per the Form 356h, new manufacturing facility is not ready for inspection until end of June 2020*

The sponsor provides this in response to an IR. The IR response is dated 9/20/2019. They state in the document:

Effective August 29, 2019, the new owner for the application referenced above is Hikma Pharmaceuticals USA Inc. (Hikma). Hikma acquired ownership of this application from Insys Therapeutics, Inc. Hikma commits to honoring the agreements, promises and conditions made by Insys Therapeutics, Inc. and will advise the FDA of any changes in the conditions in the application....Hikma is currently in the process of transferring equipment and manufacturing processes to WWCI. The analytical methods are also being transferred to WWCI at this time with the exception of the testing performed by outside labs as indicated in the application.

Therefore, the proposed manufacturer Insys will not be inspected as part of this submission, the review of the West-Ward Columbus Inc. will be provided below.

The facilities involved in the manufacture, testing, packaging, stability testing, and release of Naloxone Nasal Spray are provided in Table 1.

Table 1: Sites and Responsibilities in Manufacture of Naloxone Nasal Spray

Site Name	Site Address	Facility Establishment Indicator (FEI)	Manufacturing Operations
Insys Manufacturing, LLC	2700 Oakmont Dr. Round Rock, TX 78665, USA	3011419064	- Control and release of all components (API, excipients, packaging items) (b) (4) solution manufacturing - Testing of bulk solution - Primary and secondary packaging - Release for shipping - Shipping
Insys Development Company, Inc.	444 S. Ellis St. Chandler, AZ 85224, USA	3006646520	Release and stability testing of Naloxone Nasal Spray drug product ^a
(b) (4)			

^a Insys Development Company, Inc. performs all finished product testing for release control and stability studies except for microbiological testing

The sponsor also provided the workflow between manufacturers in document: naloxone-function-responsibilities



(b) (4)

Reviewer Note:

Based on this information the manufacturing firm(s) that will require a QS review is Insys Manufacturing LLC. They are primarily responsible for device assembly and are the final finished device manufacturer.

Of note, previous CDRH reviewer Rumi Young recommended a device cGMP pre approval inspection for both:

- Insys Manufacturing
- Insys Development Company, Inc.

Update 10/1/2019

See the Section 4.3 where the device manufacturers are changed mid-review.

Firm Name:	Insys Manufacturing
Address:	2700 Oakmont Dr. Round Rock, TX 78665, USA
FEI:	3011419064
Responsibilities:	Control and release of all components (API, excipients, packaging items), (b) (4) solution manufacturing, testing of (b) (4) solution, primary and secondary packaging, release for shipping and shipping

Inspectional History

An analysis of the firm's inspection history over the past 2 years:

- ☒ Inspection was conducted 8/21/2017 to 9/12/2017. The inspection covered drug CGMP and was classified VAI.
- ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.
- ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

A pre-approval inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm.

Update 10/1/2019

See the Section 4.3 where the device manufacturers are changed mid-review.

Firm Name:	Insys Development Company, Inc.
Address:	444 S. Ellis St. Chandler, AZ 85224 USA
FEI:	3006646520
Responsibilities:	Release and stability testing of Naloxone Nasal Spray drug product

Inspectional History

An analysis of the firm's inspection history over the past 2 years:

- ☒ Inspection was conducted 4/9/2018 to 4/12/2018. The inspection covered drug CGMP and was classified VAI.
- ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.
- ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

A pre-approval inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, a recent medical device inspection of the firm

Update 10/1/2019

See the Section 4.3 where the device manufacturers are changed mid-review.

4.3. Facilities Information (After 9/20/2019)

The sponsor provided a notification to the Agency on 9/20/2019, stating that the device manufacturer/assembler was being changed. See the new product manufacturers:

Establishment Information for the Finished Dosage Manufacturer and All Outside Contract Testing Laboratories

Establishment Name	Contact Person's Information	Address, DUNS and FEI Numbers	Functions Performed at Each Site
West-Ward Columbus Inc. cGMP Certification	Julie Hill Senior Director, Quality West-Ward Columbus Inc. Telephone: (614) 276-4000, ext. 2077 Email: jhill@Hikma.com	1809 Wilson Road (b) (4) Columbus, Ohio 43228 DUNS: 058839929 FEI: 1510690	(b) (4) Product manufacturing, packaging, and labeling will be performed (b) (4) Drug product microbiological testing may also be performed at (b) (4) an alternate testing facility to (b) (4)
Hikma Pharmaceuticals USA Inc. cGMP Certification	Jerald Andry, PharmD, MS Senior Director, Drug Regulatory Affairs and Medical Affairs Telephone: (614) 241-4154 Email: dra-columbus@Hikma.com	1809 Wilson Road Columbus, Ohio 43228 DUNS: 080189610	Application Holder
(b) (4)			

West-Ward Columbus Inc. is a wholly-owned subsidiary of Hikma Pharmaceuticals PLC and is the manufacturer and packager for Hikma Pharmaceuticals USA Inc.

Firm Name:	West-Ward Columbus Inc.
Address:	1809 Wilson Road (b) (4), Columbus, Ohio, USA
FEI:	1510690 (DUNS #058839929)
Responsibilities:	(b) (4) Product manufacturing, packaging, and labeling will be performed (b) (4). Drug product microbiological testing may also be performed at (b) (4) an alternate testing facility (b) (4).
<u>Inspectional History</u> An analysis of the firm's inspection history over the past 2 years: ☒ An analysis of the firm's inspection history over the past 2 years showed that it has not been inspected. The most recent inspection was conducted 10/17/2016 to 10/21/2016. The inspection covered drug CGMP (preapproval inspection), included device cGMP (CAPA, Design, Management and Production and Process Controls (including purchasing controls) and was classified OAI. The inspection covered the following products: non-sterile liquid and oral dosages including metered dose and dry powder inhalers). The 483 Form and EIR memo were obtained from OSAR from the 2016 inspection. The device related items that were cited under the 483 Form are the following:	

Inspection Recommendation:

A pre-approval inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, a recent medical device inspection (within the last 2 years) of the firm was not completed. Additionally, the most recent medical device cGMP inspection was categorized OAI and had major device related violations

Update 12/18/2020:

A GMP surveillance inspection was conducted on 4/1/2019 through 4/16/2019 at the firm, 1809 Wilson Road (b) (4), Columbus, Ohio, USA, FEI 1510690. This inspection was classified as VAI. The EIR memo was provided and the inspection deemed acceptable. There were no device call outs. No further PAI is necessary.

Firm Name:	Hikma Pharmaceuticals USA Inc.
Address:	1809 Wilson Road Columbus, Ohio 43228
FEI:	No FEI number provided; DUNS 080189610; Reviewer Note: FEI # based on OSAR is 3015763437.
Responsibilities:	Application Holder
<u>Inspectional History</u> An analysis of the firm's inspection history over the past 2 years: ☒ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.	
<u>Inspection Recommendation:</u> A pre-approval inspection <u>is NOT required</u> because: The firm is NOT responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part.	

4.4. 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:	
☒ High Risk of cGMP issues:	

Reviewer Comment

The product is an emergency use nasal spray. The sponsor relies on some (b) (4) controls to ensure they meet an adequate reliability. Given the indications, controls, and previous OAI inspection recommendation there is high risk of cGMP issues. See Section 10 for the full review.

Resubmission Update 12/18/2020:

Inspection was classified as VAI. Therefore, there is now a low or moderate risk of cGMP issues.

4.5. 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:	

5. LABELING

5.1. General Labeling Review

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

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A

Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

5.2. Device Specific **Labeling** Review

The instructions for use are reviewed by the lead reviewer. The instructions for use was taken from doc: ifu-proposed in Seq0000.1



(b) (4)



(b) (4)

Reviewer Comments

The labeling appears appropriate. It will be further analyzed as part of the human factors review.

5.3. Labeling Review Conclusion

LABELING REVIEW CONCLUSION

Reviewer Recommendation:

The device labeling is adequate

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		

6.2. Design Inputs and Outputs

Essential Performance Requirements

The following is taken from documents:

- 0000.3.2.P.5.1 – doc: specifications
- 0000.3.2.P.2 – doc: container-closure-system

Reviewer Comments

- The sponsor has provided a dFMEA risk analysis that is specific to the device constituent that is provided by the device manufacturer, (b) (4) in document dFMEA. This does not include risks or risk mitigations that are introduced by the drug product.

Update 12/16/2019:

This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. **See CR deficiencies.**

Update 12/18/2020:

The sponsor provided a dFMEA, UFMEA, hazard analysis and risk management report for the full combination product in response to the CR deficiency (Module 3.2.P.7).

- It is unclear if the to-be-marketed version of the device was clinically validated.

Update 12/16/2019:

The sponsor has stated in response to MC deficiencies that the device is identical to that which was used in the pivotal/BE clinical study to clinically validate the device. This is adequate.

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)	Notes:
Spray Actuation Content (Delivered Dose) Sponsor states: Results must comply at T0 and stability	Target Spray Weight: (b) (4) Mean of (b) (4) units should be within $\pm 15\%$ of the target weight and none of the individual units is outside $\pm (b) (4)\%$ of the target weight	CDER Nasal Spray Guidance suggests the following specification for nasal sprays: <i>In general, pump spray weight delivery acceptance criteria should control the weight of the individual sprays to within</i>

		15 percent of the target weight and their mean weight to within "10 percent of the target weight. <u>Note:</u> This is not aligned with the Guidance and the Sponsor does not justify sample size of (b) (4) units. In 3.2.p.5.6, The sponsor does not justify the dose accuracy specification. This should be provided. See CR deficiencies. The sponsor has committed to testing 20 units at release and through stability to achieve a greater level of confidence/reliability
Spray Content Uniformity	Tier 1: The amount of active ingredient per determination is outside of (b) (4) of label claim for not more than 1 of 10 determinations from 10 containers, (2) none of the determinations is outside of (b) (4) of the label claim, and (3) the mean of (b) (4) containers is not outside of (b) (4) of label claim. If the above acceptance criteria are not met because 2 to 3 of the 10 determinations are outside of (b) (4) of the label claim, but none are outside of (b) (4) of label claim and the mean is not outside of (b) (4) of label claim, an additional 20 containers should be sampled for second-tier testing. Tier 2: The amount of active ingredient per determination is not outside of (b) (4) of the label claim for more than 3 of all 30 determinations, (2) none of the 30 determinations is outside of (b) (4) of label claim, and (3) the mean is not outside (b) (4) of label claim.	This is aligned with the CDER nasal spray guidance. This is adequate and no further justification is required.
Spray Pattern	Ovality not more than (b) (4)	
Droplet Size Distribution	D10 not less than (b) (4) D50 not less than (b) (4) D90 not less than (b) (4)	
Plume Geometry	The sponsor does not include a specification for plume geometry; however it was measured at release and stability. They state: <i>The plume geometry of Naloxone Nasal Spray was characterized as recommended by the Nasal Spray Guidance. Measurements of plume angle and plume width were obtained for the formulations of Naloxone 8 mg/spray with 20% and Naloxone 8 mg/spray with (b) (4) % alcohol</i>	While the sponsor provides plume geometry there is no specification to determine acceptability. <u>Note:</u> They should provide a specification and ensure that this testing is met at lot release to ensure consistent device performance. See CR deficiencies. Per the Nasal Spray Guidance, plume geometry does not require a (b) (4) specification if it is well described in stability/release testing
Actuation Force Note: not included in 3.2.P.5.1	The sponsor does not include a true <u>specification for Actuation force</u>: See below	While the sponsor provides actuation force testing after product stability, they do not provide a specification.

	The actuation force needed is consistent over the stability storage conditions for six primary stability lots and demonstrate consistency of device quality over different lots of device components. The values range between (b) (4)	<u>Note:</u> They should provide a specification and verify that this specification is met. See CR deficiencies. The mean of the 20 individual units is between (b) (4), with no individual unit > (b) (4). The sponsor updated the specification in IR#3 to be < (b) (4)
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Reviewer Comments

- The sponsor appear to provide actuation force testing after stability but does not does not include an actuation force specification. The specification should be based upon the device user needs/design input. The sponsor states a (b) (4) “specification is needed: Actuation force of approximately (b) (4) which corresponds to: possible to actuate by a wide range of population including youth, adults, and elderly, but resistant to accidental actuation. Consistent among different lots and throughout the expiry period.

The sponsor should define a specification and verify/validate that the specification is appropriate for the intended users. Of note, the intended users include adults and pediatrics.

Update 12/16/2019:

This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore, the sponsor will need to provide to this deficiency as part of the CR letter. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission (Module 3.2.P.5.6). The sponsor has updated the proposed drug product release specification limit for actuation force as follows, the mean of the 20 individual units is between (b) (4) with no individual unit > (b) (4). The sponsor has provided an analytical procedure to verify the device actuation force of the drug product (Module 3.2.P.5.2). The sponsor updated the specification in IR#3 to be < (b) (4). However, the sponsor has not adequately validated that the upper specification for pediatric use. **Therefore, at this time, the device is not indicated for use by pediatrics.**

- Likewise, the sponsor has provided testing of plume geometry testing after release and to the product shelf life, but does not define a specification.

Update 12/16/2019:

This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission. “Hikma notes that plume geometry has been well characterized through the testing of registration batches on release and stability, therefore should not be included on the proposed drug product specification.”

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	NO – RISK ANALYSIS NOT FOR COMBINATION PRODUCT Y - Risk Analysis was provided for the combination product
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Yes – doc: container-closure-system – Report CH.0142
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Provides documentation aligned with Guidance Recommendations
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"	Provides documentation aligned with Guidance Recommendations
Applying Human Factors and Usability Engineering to Medical Devices	Provides documentation aligned with Guidance Recommendations

6.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION
Reviewer Recommendation The design control information is not adequate Update 12/18/2020: The sponsor responded to the CR deficiencies in their re-submission.

7. RISK ANALYSIS

7.1. Risk Management Plan

The sponsor has provided a risk analysis in document: dFMEA. This document is referenced in document: container-closure-system (3.2.P.2). The sponsor has provided a dFMEA risk analysis that is specific to the device constituent that is provided by the device manufacturer, (b) (4), in document dFMEA. This risk analysis is in accordance with ISO 14971, but this does not include risks or risk mitigations that are introduced by the drug product. Of note the information provided by the sponsor appears appropriate.

Reviewer Comments

A new risk analysis that includes the combination product risks (not solely specific to the device), is being requested.
See risk analysis deficiency)

Update 12/16/2019:

This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

7.2. Hazard Analysis and Risk Summary Report

Reviewer Comments

Not being analyzed until risk analysis of combination product is provided.

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

7.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION

Reviewer Recommendation

The risk analysis is adequate.

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)	<u>Validation</u> (Y/N)	Primary Verification Acceptable (Y/N)	Verification Shelf Life (Y/N)	Verification Shipping/Transportation (Y/N)
Spray Actuation Content (Dose Delivered) – Sponsor states input was defined in accordance with FDA Guidance Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products.	Target Spray Weight (b) (4) (20% alcohol formulation) Mean of (b) (4) units should be within $\pm 15\%$ of the target weight and none of the individual units is outside $\pm (b) (4)\%$ of the target weight <u>NOTE</u> : Not in line with CDER Spec in guidance. See CR deficiencies.	Yes	Yes*	Yes*	Yes*	Yes*
Spray Content Uniformity	Tier 1 Testing: Amount of API per container is not outside of (b) (4) (b) (4) of label claim for more than one container. None of the container is outside of (b) (4) of label claim and mean for the (b) (4) containers is not outside (b) (4) of label claim. This is aligned with CDER Guidance.	Yes	Yes	Yes	Yes	Yes
Droplet Size Distribution	At (b) (4) - D ₁₀ NLT (b) (4) D ₅₀ NLT D ₉₀ NLT	Yes	Yes	Yes	Yes	Yes
Spray Pattern	Ovality (b) (4)) NMT (b) (4)	Yes	Yes	Yes	Yes	Yes
Plume Geometry	<u>NOTE</u> : The sponsor does not include a	No **	No **	No **	No **	No**

	specification in 3.2.P.5.1. See CR deficiencies.					
Actuation Force	NOTE: The sponsor does not include a specification in 3.2.P.5.1. See CR deficiencies.	No **	No	No **	No **	No**

Reviewer Comment:

*Pending discussion of specification for dose accuracy and assuming the specification was clinically validated.

**The sponsor does not include specifications for plume geometry or actuation force.

8.1.2. Evaluation of EPR Testing

8.1.2.1.Spray Content (Delivered Dose)

Title:	Spray Content (Delivered Dose)																								
Scope/Objective & Acceptance Criteria:	Testing to verify delivered dose Acceptance Criteria: Target Spray Weight: (b) (4) (20% alcohol formulation) Mean of (b) (4) units should be within $\pm 15\%$ of the target weight and none of the individual units is outside $\pm (b) (4)\%$ of the target weight																								
Methods	Doc: analytical-procedures states: <i>The test is performed by gravimetric measurement of loss of product upon actuation using an automated actuator.</i>																								
Results: Primary Verification	The sponsor provides primary verification testing of dose delivered. This is Seq0000.3.2.p.5.4: doc: batch-analyses <table border="1" data-bbox="505 1272 1583 1465"> <thead> <tr> <th rowspan="3">Parameter</th><th rowspan="3">Acceptance Criteria</th><th>Strength</th><th colspan="3">8mg/Spray (20%w/w Alcohol)</th></tr> <tr> <th>Lot #</th><th>10261017</th><th>10271017</th><th>10361017</th></tr> <tr> <th>Date of manufacture</th><th>October 17, 2017</th><th>October 23, 2017</th><th>November 26, 2017</th></tr> </thead> <tbody> <tr> <td>Spray Actuation Content</td><td>Target Spray Weight: (b) (4) 20% alcohol formulation Mean of (b) (4) units should be within $\pm 15\%$ of the target weight and none of the individual units is outside $\pm (b) (4)\%$ of the target weight</td><td>Mean= (b) (4) %RSD (b) (4) High = Low =</td><td>Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =</td><td>Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =</td><td>Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =</td></tr> </tbody> </table> The mean/high and low dose delivered meet specification. <u>Update 12/16/2019:</u> This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. See CR deficiencies. <u>Update 12/18/2020:</u> The sponsor responded to the CR deficiencies in their re-submission.					Parameter	Acceptance Criteria	Strength	8mg/Spray (20%w/w Alcohol)			Lot #	10261017	10271017	10361017	Date of manufacture	October 17, 2017	October 23, 2017	November 26, 2017	Spray Actuation Content	Target Spray Weight: (b) (4) 20% alcohol formulation Mean of (b) (4) units should be within $\pm 15\%$ of the target weight and none of the individual units is outside $\pm (b) (4)\%$ of the target weight	Mean= (b) (4) %RSD (b) (4) High = Low =	Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =	Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =	Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =
Parameter	Acceptance Criteria	Strength	8mg/Spray (20%w/w Alcohol)																						
		Lot #	10261017	10271017	10361017																				
		Date of manufacture	October 17, 2017	October 23, 2017	November 26, 2017																				
Spray Actuation Content	Target Spray Weight: (b) (4) 20% alcohol formulation Mean of (b) (4) units should be within $\pm 15\%$ of the target weight and none of the individual units is outside $\pm (b) (4)\%$ of the target weight	Mean= (b) (4) %RSD (b) (4) High = Low =	Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =	Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =	Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =																				
Results: Shelf Life Verification	The sponsor provides reference to shelf life verification in document "container-closure". This provides a link to document stability-summary. The sponsor provides the summary stability testing results in doc: "stability-data". This includes accelerated data that appear to																								

	verify the dose accuracy to the current specification using the 20% alcohol lots at 24 months (using accelerated methods); however, it is unclear if the devices used in these stability lots are different than the to-be-marketed lots. <u>Update 12/16/2019:</u> The sponsor has clarified in the response to MC deficiencies that the devices used in the stability lots can be leveraged to support the final to-be-marketed product. The components used from the same suppliers, the design specifications are unchanged, etc. This is adequate. See Section 11, where this was described in more detail.
Results: Transportation Verification	The sponsor provides reference to the transportation study that was completed: <i>The shipping study using the final tertiary packaging was executed as per ASTM D-4169-16 standards. Packaged devices subjected to shipping test were inspected for any physical damage and tested for spray characteristics. None of the devices were damaged and all the spray characteristics were within specifications demonstrating robustness of the packaging during the shipping operation.</i> The sponsor states that the 20% alcohol version of the product (to be marketed) was used in the transportation study. The sponsor references doc: Report.CH.0142 which contains the transportation test report. Of note this testing tests for the following device EPRs: • Spray Actuation Content • Spray Content Uniformity • Spray Pattern • Droplet Size distribution Reviewer Note: This does not include activation force or plume geometry. <u>Update 12/16/2019:</u> This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. See CR deficiencies. The sponsor states that testing was conducted per ASTM D4169-16 and packages were subject to manual drop, stacking, vibration, exposure to low pressure. The summary results are included below. The sponsor tested a total of (b) (4) devices randomly chosen from 4 shippers.

Table 5: Spray Content Uniformity/Spray Actuation Content

Device	SAC (By weight)	SCU
S1-C2-D2	(b) (4)	(b) (4)
S1-C12-D2		
S2-C7-D1		
S2-C10-D1		
S2-C11-D1		
S3-C2-D1		
S3-C5-D2		
S4-C3-D2		
S4-C8-D2		
S4-C12-D1		
Mean		
%RSD		
Max		
Min		

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

**Conclusions/ Reviewer
Comments:**

Specific to Dose Accuracy:

In 3.2.p.5.6, The sponsor does not justify the dose accuracy specification; as this is not aligned with the CDER Nasal Spray Guidance, which states:

In general, pump spray weight delivery acceptance criteria should control the weight of the individual sprays to within 15 percent of the target weight and their mean weight to within "10 percent of the target weight.

The sponsor's specification is the following:

Mean of (b) (4) units should be within $\pm 15\%$ of the target weight and none of the individual units is outside $\pm (b) (4)\%$ of the target weight.

This will be brought up at the OND/OPQ MC meeting; however, it is unclear if this is acceptable. The sponsor does not justify the specification in doc: justification-of-specifications. In this document they state:

The specification is based on the Nasal Spray guidance for small volume unit dose spray products. During product development, both product release and stability data were collected. Results indicated that spray actuation content is well controlled throughout long term storage and is independent of product storage orientation and strength. This test will be performed for release and stability testing of commercial batches.

Upon review of the Guidance, it states that volumes under $\sim 20 \mu\text{L}$, other acceptance criteria can be justified; however, the dose delivered for this device is $\sim 100 \mu\text{L}$. The sponsor will need to demonstrate the specification was clinically validated. Additionally, it is unclear how a sample size of (b) (4) is appropriate.

Update 12/16/2019:

This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

Acceptable:	No
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8.1.2.2.Spray Content Uniformity

Title:	Spray Content Uniformity																							
Scope/Objective & Acceptance Criteria:	Testing to verify SCU Specification: Tier 1 Testing: Amount of API per container is not outside of (b) (4) % of label claim for more than one container. None of the container is outside of (b) (4) % of label claim and mean for the (b) (4) containers is not outside (b) (4) % of label claim. Of note this is aligned with the CDER Guidance for Nasal Sprays.																							
Methods	The sponsor states that Spray Content Uniformity is completed “by determining drug content by HPLC assay of the spray content collected during the spray actuation content testing.” The description is provided in document: CH.0113. It appears to use HPLC to measure SCU. This appears appropriate.																							
Results: Primary Verification	Document – batch analysis in Seq0000.3.P.5.4 <table><tr><th rowspan="3">Parameter</th><th rowspan="3">Acceptance Criteria</th><th>Strength</th><th colspan="3">8mg/Spray (20%w/w Alcohol)</th></tr><tr><th>Lot #</th><th>10261017</th><th>10271017</th><th>10361017</th></tr><tr><th>Date of manufacture</th><th>October 17, 2017</th><th>October 23, 2017</th><th>November 26, 2017</th></tr><tr><td>Spray Content Uniformity</td><td>Tier 1 Testing: Amount of API per container is not outside of (b) (4) of label claim for more than one container. None of the container is outside of (b) (4) of label claim and mean for the (b) (4) containers is not outside (b) (4) of label claim. (See Footnote)*</td><td>Mean= (b) (4) (n= (b) (4)) %RSD= (b) (4) High = (b) (4) Low = (b) (4)</td><td>Mean= (b) (4) (n=20) %RSD= (b) (4) High = (b) (4) Low = (b) (4)</td><td>Mean= (b) (4) (n= (b) (4)) %RSD= (b) (4) High = (b) (4) Low = (b) (4)</td></tr></table> Testing meets specification. All passed.					Parameter	Acceptance Criteria	Strength	8mg/Spray (20%w/w Alcohol)			Lot #	10261017	10271017	10361017	Date of manufacture	October 17, 2017	October 23, 2017	November 26, 2017	Spray Content Uniformity	Tier 1 Testing: Amount of API per container is not outside of (b) (4) of label claim for more than one container. None of the container is outside of (b) (4) of label claim and mean for the (b) (4) containers is not outside (b) (4) of label claim. (See Footnote)*	Mean= (b) (4) (n= (b) (4)) %RSD= (b) (4) High = (b) (4) Low = (b) (4)	Mean= (b) (4) (n=20) %RSD= (b) (4) High = (b) (4) Low = (b) (4)	Mean= (b) (4) (n= (b) (4)) %RSD= (b) (4) High = (b) (4) Low = (b) (4)
Parameter	Acceptance Criteria	Strength	8mg/Spray (20%w/w Alcohol)																					
		Lot #	10261017	10271017	10361017																			
		Date of manufacture	October 17, 2017	October 23, 2017	November 26, 2017																			
Spray Content Uniformity	Tier 1 Testing: Amount of API per container is not outside of (b) (4) of label claim for more than one container. None of the container is outside of (b) (4) of label claim and mean for the (b) (4) containers is not outside (b) (4) of label claim. (See Footnote)*	Mean= (b) (4) (n= (b) (4)) %RSD= (b) (4) High = (b) (4) Low = (b) (4)	Mean= (b) (4) (n=20) %RSD= (b) (4) High = (b) (4) Low = (b) (4)	Mean= (b) (4) (n= (b) (4)) %RSD= (b) (4) High = (b) (4) Low = (b) (4)																				
Results: Shelf Life Verification	The sponsor provides reference to shelf life verification in document “container-closure”. This provides a link to document stability-summary. The sponsor provides the summary stability testing results in doc: “stability-data”. This includes accelerated data that appear to verify the SCU to the current specification using the 20% alcohol lots at 24 months (using accelerated methods); however, it is unclear if the devices used in these stability lots are different than the to-be-marketed lots. See comment about stability lots. The sponsor states that one (b) (4) % alcohol product did not pass testing, but all of the 20% alcohol products did. Since the sponsor is only proposing to market the 20% alcohol product, I believe that this is acceptable.																							
Results: Transportation Verification	See dose Spray Content above. SCU passed in this testing.																							
Conclusions/ Reviewer Comments:	See Reviewer’s Comments Above																							
Acceptable:	☐ Yes ☐ No																							

8.1.2.3.Droplet Size Distribution

Title:	Droplet Size Distribution					
Scope/Objective & Acceptance Criteria:	Testing to verify DSD					
	Specification (at (b) (4)):					
	D ₁₀ (10% of droplets) NLT (b) (4)					
	D ₅₀ (50% of droplets) NLT (b) (4)					
	D ₉₀ (90% of droplets) NLT (b) (4)					
Methods	Droplet Size Distribution protocol was provided in document CH.0175. The sponsor appears to use a laser diffraction setup. This appears appropriate					
Results: Primary Verification	Parameter		Acceptance Criteria	Strength	8mg/Spray (20%w/w Alcohol)	
				Lot #	10261017	10271017
				Date of manufacture	October 17, 2017	October 23, 2017
					10361017	
	Droplet Size Distribution by Laser Diffraction		D ₁₀ not less than (b) (4)	(b) (4)		
			D ₅₀ not less than (b) (4)			
			D ₉₀ not less than (b) (4)			
			Span-Report Results			
	Reviewer Note:					
	It is noted that the sponsor conducted testing of DSD at (b) (4) but only provided a specification for DSD at (b) (4). They should state why a specification is not needed at (b) (4); despite their testing and what the significance is of only providing a spec at (b) (4).					
Update 12/16/2019:						
This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. See CR deficiencies.						
Update 12/18/2020:						
The sponsor responded to the CR deficiencies in their re-submission.						
Results: Shelf Life Verification	The sponsor provides the summary results and states that all product met specification; however, it is unclear if the devices used in these stability lots are different than the to-be-marketed lots. See comment about stability lots.					
Results: Transportation Verification	See the description of the transportation study that was described in the Spray Content results discussion in Section 8.1.2.1. The sponsor provides the summary data for DSD and each passed:					
	Table 1: (b) (4) from Laser beam					
	Device	Dv10 (um)	Dv50 (um)	Dv90 (um)	Span (b) (4)	
	S2-C1-D2*	(b) (4)				
	S2-C5-D1					
	S4-C2-D2					
	Average					
	Table 2: (b) (4) from Laser beam					
	Device	Dv10 (um)	Dv50 (um)	Dv90 (um)	Span (b) (4)	
	S1-C2-D1	(b) (4)				
	S3-C1-D2					
	S3-C9-D1					
	Average					
Conclusions/ Reviewer Comments:	See Reviewer's Comments Above					

Acceptable:	☐ Yes ☐ No
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8.1.2.4.Spray Pattern

Title:	Spray Pattern Review																																												
Scope/Objective & Acceptance Criteria:	Testing to verify Spray Pattern Acceptance Criteria Ovality not more than (b) (4)																																												
Methods	Methods were provided in CH.0176. Sponsor uses an optical/camera method to analyze ovality																																												
Results: Primary Verification	<table border="1"> <thead> <tr> <th rowspan="2">Parameter</th><th rowspan="2">Acceptance Criteria</th><th>Strength</th><th colspan="3">8mg/Spray (20%w/w Alcohol)</th></tr> <tr> <th>Lot #</th><th>10261017</th><th>10271017</th><th>10361017</th></tr> <tr> <th colspan="2"></th><th>Date of manufacture</th><th>October 17, 2017</th><th>October 23, 2017</th><th>November 26, 2017</th></tr> </thead> <tbody> <tr> <td>Spray Pattern^b</td><td> Dmin (mm)-Report Results Dmax (mm)-Report Results Ovality- NMT (b) (4) </td><td colspan="4">(b) (4)</td></tr> </tbody> </table> The ovality meet the acceptance criteria.					Parameter	Acceptance Criteria	Strength	8mg/Spray (20%w/w Alcohol)			Lot #	10261017	10271017	10361017			Date of manufacture	October 17, 2017	October 23, 2017	November 26, 2017	Spray Pattern ^b	Dmin (mm)-Report Results Dmax (mm)-Report Results Ovality- NMT (b) (4)	(b) (4)																					
Parameter	Acceptance Criteria	Strength	8mg/Spray (20%w/w Alcohol)																																										
		Lot #	10261017	10271017	10361017																																								
		Date of manufacture	October 17, 2017	October 23, 2017	November 26, 2017																																								
Spray Pattern ^b	Dmin (mm)-Report Results Dmax (mm)-Report Results Ovality- NMT (b) (4)	(b) (4)																																											
Results: Shelf Life Verification	The sponsor provides the summary results and states that all product met specification; they state: <i>In the 20% w/w Alcohol formulation batches (b) (4) data), the minimum (Dmin) dimension ranged from (b) (4), the maximum (Dmax) dimension ranged from (b) (4) and the ovality ranged from (b) (4). For data at the (b) (4), the minimum (Dmin) dimension ranged from (b) (4), the maximum (Dmax) dimension ranged from (b) (4), and the ovality ranged from (b) (4). No trends were apparent in the data with respect to storage condition, orientation, or time point.</i> It is unclear if the devices used in these stability lots are different than the to-be-marketed lots. See comment about stability lots.																																												
Results: Transportation Verification	See the description of the transportation study that was described in the Spray Pattern results discussion in Section 8.1.2.1. The sponsor provides the summary data for DSD and each passed: Table 3: (b) (4) from Laser beam <table border="1"> <thead> <tr> <th>Device</th><th>Dmin (mm)</th><th>Dmax (mm)</th><th>Ovality</th></tr> </thead> <tbody> <tr> <td>S2-C11-D2</td><td colspan="3">(b) (4)</td></tr> <tr> <td>S2-C2-D2</td><td colspan="3">(b) (4)</td></tr> <tr> <td>S4-C10-D1</td><td colspan="3">(b) (4)</td></tr> <tr> <td>Average</td><td colspan="3">(b) (4)</td></tr> </tbody> </table> Table 4: (b) (4) from Laser beam <table border="1"> <thead> <tr> <th>Device</th><th>Dmin (mm)</th><th>Dmax (mm)</th><th>Ovality</th></tr> </thead> <tbody> <tr> <td>S1-C12-D1</td><td colspan="3">(b) (4)</td></tr> <tr> <td>S3-C3-D1</td><td colspan="3">(b) (4)</td></tr> <tr> <td>S3-C7-D1</td><td colspan="3">(b) (4)</td></tr> <tr> <td>Average</td><td colspan="3">(b) (4)</td></tr> </tbody> </table>					Device	Dmin (mm)	Dmax (mm)	Ovality	S2-C11-D2	(b) (4)			S2-C2-D2	(b) (4)			S4-C10-D1	(b) (4)			Average	(b) (4)			Device	Dmin (mm)	Dmax (mm)	Ovality	S1-C12-D1	(b) (4)			S3-C3-D1	(b) (4)			S3-C7-D1	(b) (4)			Average	(b) (4)		
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Conclusions/ Reviewer Comments:	See Reviewer's Comments Above																																												
Acceptable:	☐ Yes ☐ No																																												

8.1.2.5. Plume Geometry

Title:	Plume Geometry Review																																																																																																									
Scope/Objective & Acceptance Criteria:	Testing to verify Plume Geometry <u>Acceptance Criteria:</u> Sponsor does not define a specification, but they provide testing to demonstrate consistency. A specification should be provided since the sponsor See MC deficiency. <u>Update 12/16/2019:</u> This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. See CR deficiencies. <u>Update 12/18/2020:</u> The sponsor responded to the CR deficiencies in their re-submission.																																																																																																									
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Results: Primary Verification	See shelf life testing -																																																																																																									
Results: Shelf Life Verification	Sponsor provides shelf life testing for plume geometry: Table 2: Naloxone Nasal Spray - Plume Geometry Characterization <table><tr><th rowspan="2">Formulation</th><th rowspan="2">Lot#</th><th colspan="4">40°C/75%RH</th><th colspan="4">25°C/60%RH</th></tr><tr><th>Time point</th><th>Orientation</th><th>Plume Angle (°)</th><th>Plume Width (mm)</th><th>Time point</th><th>Orientation</th><th>Plume Angle (°)</th><th>Plume Width (mm)</th></tr><tr><td rowspan="18">Naloxone Nasal Spray, 20% alcohol formulation</td><td rowspan="12">162343</td><td>T=0</td><td>N/A</td><td rowspan="12">(b) (4)</td><td rowspan="12">(b) (4)</td><td>T=0</td><td>N/A</td><td rowspan="12">(b) (4)</td><td rowspan="12">(b) (4)</td></tr><tr><td>1M</td><td>Upright</td><td>3M</td><td>Upright</td></tr><tr><td></td><td>Horizontal</td><td></td><td>Horizontal</td></tr><tr><td>2M</td><td>Upright</td><td>6M</td><td>Upright</td></tr><tr><td></td><td>Horizontal</td><td></td><td>Horizontal</td></tr><tr><td>3M</td><td>Upright</td><td>9M</td><td>Upright</td></tr><tr><td></td><td>Horizontal</td><td></td><td>Horizontal</td></tr><tr><td>6M</td><td>Upright</td><td>12M</td><td>Upright</td></tr><tr><td></td><td>Horizontal</td><td></td><td>Horizontal</td></tr><tr><td></td><td></td><td>18M</td><td>Upright</td></tr><tr><td></td><td></td><td></td><td>Horizontal</td></tr><tr><td rowspan="6">10261017</td><td>T=0</td><td>N/A</td><td>T=0</td><td>N/A</td></tr><tr><td>1M</td><td>Upright</td><td>3M</td><td>Upright</td></tr><tr><td></td><td>Horizontal</td><td></td><td>Horizontal</td></tr><tr><td>2M</td><td>Upright</td><td>6M</td><td>Upright</td></tr><tr><td></td><td>Horizontal</td><td></td><td>Horizontal</td></tr><tr><td>3M</td><td>Upright</td><td></td><td></td></tr><tr><td></td><td>Horizontal</td><td></td><td></td></tr><tr><td>6M</td><td>Upright</td><td></td><td></td></tr><tr><td></td><td>Horizontal</td><td></td><td></td></tr></table>	Formulation	Lot#	40°C/75%RH				25°C/60%RH				Time point	Orientation	Plume Angle (°)	Plume Width (mm)	Time point	Orientation	Plume Angle (°)	Plume Width (mm)	Naloxone Nasal Spray, 20% alcohol formulation	162343	T=0	N/A	(b) (4)	(b) (4)	T=0	N/A	(b) (4)	(b) (4)	1M	Upright	3M	Upright		Horizontal		Horizontal	2M	Upright	6M	Upright		Horizontal		Horizontal	3M	Upright	9M	Upright		Horizontal		Horizontal	6M	Upright	12M	Upright		Horizontal		Horizontal			18M	Upright				Horizontal	10261017	T=0	N/A	T=0	N/A	1M	Upright	3M	Upright		Horizontal		Horizontal	2M	Upright	6M	Upright		Horizontal		Horizontal	3M	Upright				Horizontal			6M	Upright				Horizontal		
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Results: Transportation Verification	This was not evaluated after transportation. See MC deficiency <u>Update 12/16/2019:</u> This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. See CR deficiencies. <u>Update 12/18/2020:</u> The sponsor responded to the CR deficiencies in their re-submission.
Conclusions/ <u>Reviewer Comments:</u>	See Reviewer's Comments Above
Acceptable:	☐ Yes ☒ No

8.1.2.6. Actuation Force

Title:	Actuation Force Review
Scope/Objective & Acceptance Criteria:	Testing to verify Actuation Force <u>Acceptance Criteria:</u> Sponsor does not define a specification, but they provide testing to demonstrate consistency. A specification should be provided since the sponsor See MC deficiency. <u>Update 12/16/2019:</u> This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. See CR deficiencies. <u>Update 12/18/2020:</u> The sponsor responded to the CR deficiencies in their re-submission.
<u>Methods</u>	The sponsor does not provide the test methods. See MC deficiency. <u>Update 12/16/2019:</u> This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. See CR deficiencies.

	Update 12/18/2020: The sponsor responded to the CR deficiencies in their re-submission.																						
Results: Primary Verification	See shelf life testing -																						
Results: Shelf Life Verification	Sponsor provides shelf life testing for plume geometry: <table border="1"> <thead> <tr> <th>Naloxone Nasal Spray Lot</th><th>Force to Actuate (kg)</th><th>Release Data</th><th>(b) (4) 25°C/60%RH</th><th>(b) (4) 40°C/75%RH</th></tr> </thead> <tbody> <tr> <td>10261017</td><td>Avg= (b) (4) Standard Deviation</td><td colspan="3" rowspan="7"></td></tr> <tr> <td>10271017</td><td>Avg= (b) (4) Standard Deviation</td></tr> <tr> <td>10281017</td><td>Avg= (b) (4) Standard Deviation</td></tr> <tr> <td>10291017</td><td>Avg= (b) (4) Standard Deviation</td></tr> <tr> <td>10301017</td><td>Avg= (b) (4) Standard Deviation</td></tr> <tr> <td>10361017</td><td>Avg= (b) (4) Standard Deviation</td></tr> <tr> <td></td><td></td></tr> </tbody> </table> They provide activation force testing after accelerated aging to show consistency; however, there is no specification to evaluate consistency. See MC deficiency. Update 12/16/2019: This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. See CR deficiencies. Update 12/18/2020: The sponsor responded to the CR deficiencies in their re-submission.	Naloxone Nasal Spray Lot	Force to Actuate (kg)	Release Data	(b) (4) 25°C/60%RH	(b) (4) 40°C/75%RH	10261017	Avg= (b) (4) Standard Deviation				10271017	Avg= (b) (4) Standard Deviation	10281017	Avg= (b) (4) Standard Deviation	10291017	Avg= (b) (4) Standard Deviation	10301017	Avg= (b) (4) Standard Deviation	10361017	Avg= (b) (4) Standard Deviation		
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Conclusions/ Reviewer Comments:	See Reviewer's Comments Above																						
Acceptable:	☐ Yes ☒ No																						

Design Verification:

The design verification is adequate.

8.2. Reliability Verification Review

Because of the product intended use; i.e. emergency/life saving use treatment of opioid overdose, the Agency recommend that the sponsor conduct a fault tree analysis to demonstrate adequate reliability of the device components and verification of the final device.

In a type B meeting comments, the following was issued to the Sponsor: “we expect you to establish a reliability specification of at least 99.99% with 95% confidence for the successful delivery of the full intended dose of a single nasal spray unit and to verify this reliability through both design and manufacturing data analysis. We expect you to meet this reliability requirement with a single nasal spray unit, not the package of the combination product (4 devices).”

In addition boilerplate reliability comments were issued corresponding to a nasal spray emergency use device.

During the meeting the agency recommended the following for how the Sponsor could define a sample size for the product. The following is taken from the Sponsor’s meeting minutes:

FDA recommended that Insys develop a fault tree analysis with a top level failure mode of “failure to deliver the full intended dose”. The fault tree should be traced to the component assembly and dimensional elements that could result in failure to produce the full dose. FDA suggested that the sponsor could then define dimensional tolerances of the device components taking into account the individual components and their use in conjunction with associated components of the device, then utilize the incoming component testing for the device component that could affect the top level failure of “failure to deliver the full intended dose”. Insys can perform a risk analysis to identify in-coming dimensional checks and tolerances as well as possible issues during the combination product assembling process (including interaction of components) that may lead to device failure to actuate and to the top level failure “failure to deliver the full intended dose”. Based on the risk analysis, Insys can calculate the sample size needed for reliability verification. This will be an acceptable approach to FDA to define the sample size needed for reliability verification.

The device reliability will be reviewed from a component level and system level, corresponding to the FTA and design verification data. See the reviews below:

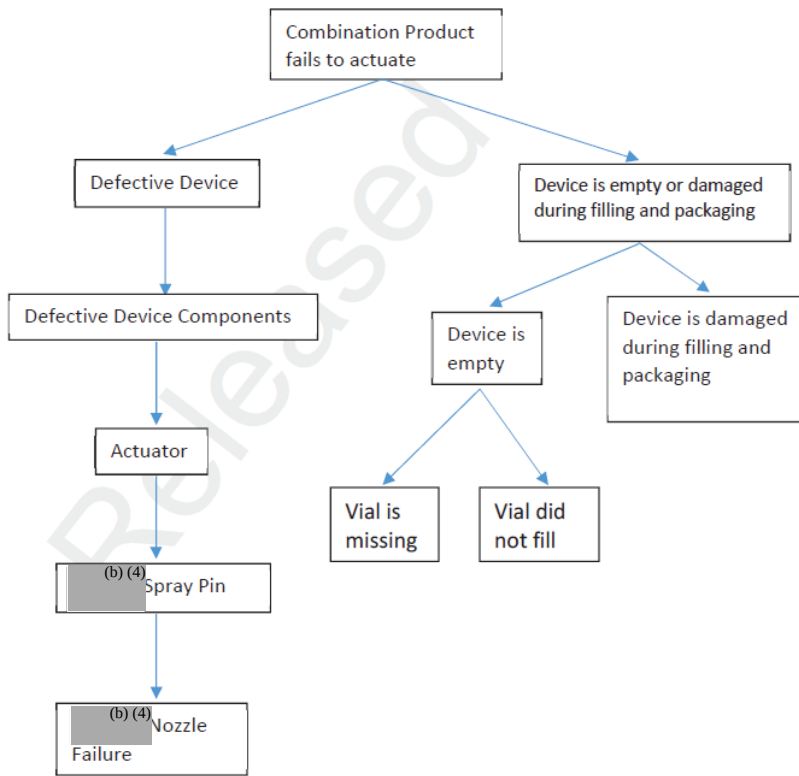
8.2.1. Fault Tree Analysis:

The purpose of the Fault tree review is to demonstrate adequate reliability mitigating the risk of “Failure to Deliver the Intended Dose” from a device component level using manufacturing data/process validation data.

The sponsor states the following in document container-closure-system

The reliability study for the Naloxone Nasal Spray drug-device combination product was designed based on input received from the FDA-CDRH. Reliability was evaluated at 99.99% with 95% confidence. Initially a fault tree analysis was completed for the defect of “device fails to actuate.” Fault tree analysis included one arm that reviewed the defect as a result of defective device components. The second arm reviewed the steps in the manufacturing process for the combination product that would result in this defect. For the device components dFMEA provided the information needed to estimate the defect rate for any individual device component defect to result in no dose. The worst-case defect rate is 1 in 15,000 which is better than 1 in 10,000 needed as per the reliability specification of 99.99%.

The sponsor provides the FTA in their reliability report in document: Report.CH.0144.



Reviewer Note:

The sponsor is attempting to leverage the reliability information from the (b) (4) Nasal Spray Device (DMF# (b) (4)) that was approved under other emergency use nasal spray products and apply it to their product.

It is understood that the device is relatively simple in terms of the number of components, but this does not address the failure modes of the actuator, (b) (4) spray pin, (b) (4) nozzle failure in terms of their interaction with each other.

They attempt to address this by providing information gathered from the device component supplier dFMEA of failure associated with the user not getting their full dose. This information is shown below:

Table 2: Device defects that would result in no dose, reviewed for the design controls and/or in-process testing controls.

Main Component	Sub-component	Defect	Control	Result*
Actuator	Cannula	Canula falls off spray pin	Cannula insertion force is controlled and verified 100% with a sensor	<1 in 15000 defects will go undetected
	Cannula	Canula moves during plunger piercing	Cannula insertion force is controlled and verified 100% with a sensor	<1 in 15000 defects will go undetected
	Cannula/Spray pin sub assembly	Cannula pierces plunger out of center axis	Cannula/spray pin sub assembly and actuator centering control is verified 100% with sensor	<1 in 15000 defects will go undetected
	Cannula	Cannula does not pierce plunger fully	Occurrence rating of improbable	≤1 in 15879 defect occurrences

Reviewer Note:

The Sponsor provides reference to an dFMEA to approximate the failure of individual components, while this approach could be reasonable; there is no data within the dFMEA to justify the probability claims. The sponsor proposes to supplement with their own measurements through incoming inspections of the components.

In addition, the failure modes that are being examined in dFMEA are functional only; not tracing down to the component level. The sponsor should be measuring the reliability of the critical component associated with each subcomponent failure in their incoming inspections/assembly process. For example, for the failure mode of cannula does not pierce plunger, it is unclear what are the sub-failure modes of this failure mode; i.e. is it cannula too short/out of spec, plunger material too rigid, etc. This should be supporting with empirical data for the reliability of each event.

They attempt to do this below with an analysis of device components that they complete at incoming inspections see below:

Table 3: Variance Analysis

Nasal Spray Device Component	In-coming testing at Insys	Mean (Based on data collected for incoming) (mm)	Lower Target Specification evaluated (mm)	Upper Target Specification evaluated (mm)	PPM Lower	PPM Upper
Actuator	Length of base	(b) (4)				
	Width of base					
Holder	Inside diameter					
	Ledge diameter					
	Overall height					
Stopper	Height					
	Rib diameter					
Vial	Bottom diameter					
	Inside diameter					
	Overall height					
	Top ledge diameter					

The sponsor then provides the associated risk with these components being higher or lower than the specification:

Table 4: Risk analysis of dimensional elements of nasal device components

Nasal Spray Device Component	In-coming testing at Insys	Test result	Risk	Controls to minimize risk
Actuator	Length of base of actuator	Higher length	Vial holder may not fit if higher length is due to height of nozzle portion	Will be rejected during combination product manufacturing
		Lower length	Vial holder may not fit if lower length is due to height of nozzle portion	Will be rejected during combination product manufacturing
	Width of base of actuator	Higher width	Vial holder may not fit if higher width is due to height of nozzle portion	Will be rejected during combination product manufacturing
		Lower width	Vial holder may not fit if lower width is due to height of nozzle portion	Will be rejected during combination product manufacturing

Nasal Spray Device Component	In-coming testing at Insys	Test result	Risk	Controls to minimize risk
Vial holder	Overall height	Taller	Vial will still fit inside the vial holder	Tighter incoming component tolerances
		Shorter	Vial will not fit completely	Combination product manufacturing machine stops, and vial holder removed
	Ledge diameter	Larger diameter	Vial holder will not be assembled	Will be rejected during combination product manufacturing
		Smaller diameter	Vial holder will slip out of actuator portion	Will be rejected during combination product manufacturing
	Inside diameter	Larger diameter	Vial may still assemble but may move inside assembled combination product-Possibility of (b) (4) penetrating stopper and formulation evaporation resulting in low dose.	Tighter incoming component tolerances
		Smaller diameter	Vial will not fully sit in the vial holder.	Combination product manufacturing machine stops, and vial holder removed
Glass vial	Overall height	Too tall	Will not fit into the vial holder	Combination product manufacturing machine stops, and vial holder removed.
		Too short	Stopper position will be higher resulting in (b) (4) penetration of stopper upon assembly-Low dose due to possible solution evaporation	Tighter incoming component tolerances
	Bottom diameter	Too wide	Will not assemble	Will be rejected during combination product manufacturing
		Too narrow	Vial may still assemble but may move inside assembled combination product-Possibility of (b) (4) penetrating stopper and formulation evaporation resulting in low dose.	Tighter incoming component tolerances
	Top ledge diameter	Too wide	Will not assemble into the actuator	Will be rejected during combination product manufacturing
		Too narrow	May still assemble properly-No effect on dose	Tighter incoming component tolerances
	Inside diameter	Too wide	Stopper will not seal the solution properly-Low dose possible	Tighter incoming component tolerances
		Too narrow	Will affect stopper placement and stopper height and	will be rejected during combination product manufacturing
Stopper	Height	Too high	(b) (4) could puncture stopper causing formulation evaporation resulting in low dose	Tighter incoming component tolerances
		Too low	May deliver lower dose	Tighter incoming component tolerances
	Rib diameter	Too wide	Will not insert into vial during combination product manufacturing	Will be rejected during combination product manufacturing
		Too narrow	Will not seal the solution properly. May result in low dose.	Tighter incoming component tolerances

From the information collected in the incoming inspections above; it does not appear that the sponsor is including checks for the cannula/spray pin assembly etc. Only the vial/stopper and the actuator and holder. They are relying very heavily on (b) (4) dFMEA to support their level of reliability. In addition do not appear to know the critical dimensions of the individual components that would result in device failure. Overall, the issue appears to be that the supplier is not sharing information with the device holder. Therefore they do not understand what component and which dimensions would result in failure of the product.

Given that the DMF device is currently approved under the Narcan NDA 208411 for emergency use Narcan, the sponsor will need to demonstrate that their manufacturing/assembly steps are ensuring 99.99% reliability as well.

Update 12/16/2019:

This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

8.2.2. Reliability Verification Testing:

Reliability is also needed from a system level in addition to the component level; therefore in a type B meeting, the Agency recommended to the sponsor to provide us device testing after preconditioning to the worst case testing. This included:

- Shipping conditions
- Aging
- Storage orientation/conditions
- Vibration
- Shock
- Actuation orientation.

The sponsor should use devised a protocol to address this evaluate device design controls as well as process validation data from the device manufacturer and utilize a statistical tolerance interval to determine the sample size.

The sponsor states the following:

Based on this feedback, Insys tested at least 480 devices each from two lots of combination product packaged in 20 shippers each to verify reliability.

Reviewer Note:

It is unclear how the sponsor decided 480 devices should be chosen for reliability verification to achieve a 99.99%/95% reliability confidence. This should be discussed.

Update 12/16/2019:

This information was requested in the MC deficiencies. The sponsor will not provide information until mid 2020; therefore the sponsor will need to provide to this deficiency as part of the CR letter. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

The sponsor provides the following protocol for preconditioning of the product prior to verification testing.

STUDY DESIGN

Testing plan

- a. Selection of Product for reliability testing: Insys has developed two formulations of Naloxone Nasal Spray. One formulation contains 20% alcohol and the second one contains (b)(4)% alcohol. For the reliability testing, one lot of each formulation was tested.
- b. For reliability testing the devices from Lots 10361017 and 10291017 were preconditioned to the following conditions in the order listed:
 - i. Aging: Samples that have been exposed to ICH accelerated storage conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\%\text{RH} \pm 5\%\text{RH}$) for at least six months were used to address aging and high temperature storage conditions.
 - ii. Shipping: After aging, the product samples were packaged in the to be marketed blister and carton packaging and subjected to shipping protocol as per ASTM D-4169-16 with emphasis on vibration simulation as well as shock handling.
 - iii. Device actuation environmental conditions: Product samples subjected to aging and shipping in i) and ii) above were actuated in the normal upright orientation. The environmental conditions during actuation were ambient, and temperature and humidity levels were recorded.
In a separate study it was determined that device orientation does not affect the actuation or dose delivered (Report.CH.0123).
The actuation force needed is controlled by the device design and cannot be varied.
 - iv. The test performed was the spray actuation content (Spray Weight) to ensure that the device actuated properly and delivered dose within the specification.

Reviewer Note:

Notes regarding the protocol:

- It is unclear if 6 months at 40 deg C is equivalent to 2 years of real time aging. See MC comments
Updated 12/18/20: The sponsor provided 24 months of real time aging to support the shelf life of 24 months.
- The sponsor used one lot of the (b)(4)% alcohol and one lot of 20% alcohol. See MC comments
Updated 12/18/20: The sponsor updated the testing to include only the 20% alcohol formulation, which is intended for commercial distribution.
- Shipping conditions were used as preconditioning. Shipping/Shock handling were used. This is appropriate
- Different storage conditions were used during aging.
- The sponsor only verifies spray actuation content and no other device EPR. This is not acceptable. Sponsor should verify all EPRs. In accordance with previous Type B meeting comments. See MC Comments.

The sponsor states that all device met the spray actuation content specification:

(b)(4) % Alcohol Product Testing:

Lot 10291017 - Spray Actuation Content (Spray Weight) Results:

A total of 473 devices were actuated using the automated actuator as per method CH.0113. All devices actuated, which conforms to the acceptance criteria for acceptable reliability testing. None of the spray weights were outside of (b) (4) of the target spray weight of (b) (4), which conforms to the acceptance criteria.

Lot 10291017	% of Target Spray Weight (b) (4)
Average	
Min	
Max	

A visual inspection of the product was completed as well. The sponsor states the following:

Of the 20 shippers that were opened, only 1 device in one shipper was found to have a loose vial holder (plunger), wherein the bridges connecting the plunger to the actuator were broken. It was suspected that the loose vial plunger would not affect functionality, so this device was actuated with the other devices for spray actuation content.

Reviewer Note:

The sponsor identifies the root cause of the failures that were identified; however they also state that they will repeat the shipping validation study to ensure that the product meets specification after shipping. Since this information, will be re-tested and provided in a future submission. This should be reviewed upon resubmission. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

Reviewer Note:

The sponsor states that all of the (b) (4) % alcohol devices passed; however this is not the to be marketed product. The sponsor should justify how this testing can be leveraged for reliability. See MC comments.

Update 12/16/2019:

the sponsor states that the (b) (4) % alcohol formulation was use to support the “robustness of the device constituents” for the purposes of the study. This is not adequate as it does not provide any sort of comparative information of drug product characteristics that would support its use in the reliability study. The sponsor should provide a scientifically sound justification for why both formulations can be used for reliability. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

20% Alcohol Product Testing

Two lots were tested for reliability (Lot #s 10361017 and 10291017). For one lot, 10 devices out of 504 inspected from 21 shippers showed vial holder separated. The damage was traced back to the root cause of shipping drop test not being performed as per the protocol. The damage was a result of higher impact during the drop test. All the devices tested including the ones where vial holder separated, actuated properly to deliver the desired dose and have no impact on the device functionality.

For the second lot all the devices actuated properly to deliver the desired dose. One device that had vial holder separated also actuated properly to deliver the dose. Results show that for devices that have aged for 8 months at 40°C/75%RH condition and subjected to shipping simulation of vibration, drop and low altitude, the device performed as designed.

There were no device failures.

As specified in the protocol, the damage to the device was reviewed and the root cause was determined to be higher impact stress applied during shipping simulation. In order to mitigate this kind of damage to the device, shipping procedures will be reviewed further, and additional controls will be added prior to commercial launch if appropriate.

Reviewer Note:

The sponsor states that 10 out of 504 devices tested from 21 shippers showed vial holder separation. The sponsor states:

The damage was traced back to the root cause of shipping drop test not being performed as per the protocol. The damage was a result of higher impact during the drop test. All the devices tested including the ones where vial holder separated, actuated properly to deliver the desired dose and have no impact on the device functionality.

This is unacceptable. See MC deficiency.

Reliability Verification:

The reliability information is adequate.

8.3. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION

Reviewer Recommendation

The design verification is adequate.

8.4. Biocompatibility Review:

CDER is responsible for the device components that are part of the fluid path. Under this review, the mucosal/skin contacting devices were evaluated per ISO 10993-1 and the ISO 10993 FDA Guidance for biocompatibility testing for medical devices. Given the amount of contact that the patient will be using the device a contact duration of less than 24 hours was used. I believe that this is adequate, given that this is an emergency use product that will not be used regularly. The sponsor identifies the actuator as the only nasal mucosa contacting device; therefore, Cytotoxicity, Sensitization, and Irritation testing was completed for the Actuator.

Reviewer Note:

Of note the sponsor identifies the spray pin as a device component where the drug product comes into contact with. They state: The spray pin, which comes into contact with the liquid drug product during use for a limited duration (e.g. a few seconds). It is unclear if this was reviewed as part of the extractables leachables study to analyze additional endpoints.

Reviewer Note to DMEPA Reviewers -(sent to CDER/OPQ CMC reviewer Jizhou Wang on 10/4/2019):

The sponsor designates the spray pin on the device as having drug product contact as part of the fluid delivery path. It is noted in their biocompatibility information that they conducted Toxicity and Irritation information, but given that there

is drug product contact as part of delivery, we believe that this should have been evaluated in the extractable/leachable study and tox risk assessment for the acute systemic endpoints. Do you know if this component was evaluated in the extractable/leachable study? If not would we be able to issue a deficiency requesting this information?

Update 10/8/2019

The lead OPQ reviewer, Jizhou Wang, stated in an email response: *Since the contact time between spray pin and drug product is transit and the PF is for one time use, we think the E/L studies may not apply.* Given this information, from the product reviewers that would review chemistry/extractables from the materials, I will defer to them and not request this information.

The sponsor provides the following information, which they state is supplied within the DMF:

Component	Nasal Mucosa Contact	Drug Product Liquid Contact	Material / Grade	Document Type
Actuator	Yes limited	Yes limited	(b) (4)	USP Test Reports: (b) (4) (b) (4) • <661> Containers : Physicochemical Tests • Cytotoxicity : <87> Biological Reactivity Test, In Vitro : Elution Test Diffusion (ISO 10993 Part 5) • Irritation <88> Biological Reactivity Test, In Vivo : USP Intracutaneous Test (ISO 10993 Part 10)
Actuator	Yes limited	Yes limited		Sensitization (Guinea Pig Maximization Test) – ISO 10993-Part 10

The sponsor has stated that they are using USP <87> and <88> for tests for Cytotoxicity and Irritation, which appear to align with the respective parts of ISO 10993. They are using ISO 10993 for Sensitization.

Reviewer Note:

The cytotoxicity, sensitization, irritation (CSI) testing should be provided by the DMF holder. This is cannot be found within the DMF.

This was requested as a mid-cycle deficiency to the DMF holder. They provided a response stating that the responses were within the paper copy of the DMF. Rather than issuing a comment requesting that they submit the information electronically for ease of review, Venkateswara Pavuluri (OPQ), insisted that this information be reviewed from the paper copy of the DMF. This was requested.

Of note, the device patient contacting components have previously been reviewed and approved under multiple NDAs for a similar contract duration. One of which is NDA 208411 – Narcan (Naloxone Hydrochloride). Given this information only a summary biocompatibility review for CSI testing will be provided below.

I have examined the paper copy of the DMF testing. See the summary review below:

Biocompatibility Test	Test Method	Summary Notes
Cytotoxicity	USP <87> - ISO 10993 -5: Elution Test Diffusion	This test report was reviewed within the DMF (b) (4) Volume 10.1 – page 385 (September 9, 2014). This appears to align with test methods recommended in ISO 10993-5 for

		in vitro cytotoxicity. The cell cultures of L-929 (mammalian fibroblast cells) were plated and allowed to grow until reaching 80% confluence; then the test article was introduced. Positive and negative controls were used as comparators. The device components did not exhibit any cytotoxic responses and reflected the outcome of the negative control.
Sensitization	ISO 10993 -10: Guinea Pig Maximization Test	Reviewer Note: The Sensitization report cannot be located; however, given that the device patient contacting components have previously been reviewed and approved under multiple NDAs for a similar contract duration. One of which is NDA 208411 – Narcan (Naloxone Hydrochloride), I am not concerned that this device would be a sensitization risk. For the purposes of the review, I believe that this adequate information for me to state that the device materials are not a sensitization risk.
Irritation	USP <88> - ISO 10993 -10: USP Intracutaneous Test	This test report was reviewed within the DMF (b) (4) Volume 10.1 – page 410 (September 9, 2014). This appears to align with test methods recommended in ISO 10993-10 for intracutaneous testing using New Zealand white rabbits. The device components did not exhibit any sensitization greater than that of the controls with an average scores of (b) (4) respectively; which indicates no edema or erythema

Biocompatibility Verification:
The biocompatibility information is adequate.

9. HUMAN FACTORS VALIDATION REVIEW

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

Reviewer Note

DMEPA did not provide a consult to CDRH; however, given the indications of emergency use, a cursory review of the intended users, critical tasks, and results were completed by the CDRH lead reviewer. I touched based with infusion TL Carolyn Dorgan regarding the lack of DMEPA consult to CDRH. She indicated that if we do not receive a consult from DMEPA then we should provide a high level review of the Human Factors material and a recommendation/comments to DMEPA. This is what is completed below.

The sponsor provides the following summary information:

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Based on conclusion of this initial risk analysis, Insys identified critical tasks associated with the use of the Naloxone Nasal Spray drug-device combination product ([User-Related Risk Analysis report](#)) and conducted a Human Factor usability study. The data from this study demonstrated that the Naloxone Nasal Spray drug-device combination product was easy to use for the intended users in a likely environment. The device and instructions were tested with a panel of thirty-one (31) subjects, including youth and persons with low-literacy levels. The test environment was designed to replicate a potential opioid overdose ([Human Factor Study INS018-2-16 \[GLM 18216\]](#)).

The sponsor provides the HF report in document: naloxone-nasal-spray-device-human-factor-study-report.

Intended Users

They state that the following regarding the users used in the study:

To replicate this diverse potential user base, the sample for this study included lay user adults ages 20 to 70 with normal literacy levels, youth ages 12 to 17, and adults with low-literacy levels. Lay users were included for this research because they represent the worst case scenario.

Reviewer Note:

The sponsor states that lay youth and adult users of varying literacy levels were used in the study. This appears appropriate to approximate the worst case.

Critical Task Analysis:

The sponsor provided their use related risk analysis in document: User-Related Risks Analysis. They provide the following tasks that are associated with use of the device:

User Task	Possible Task Failures and Use Errors	Possible Hazard / Harm Resulting from Failures/Use Errors
Opening the blister to take device	• Damage to device • Inability to open package	• Delay of therapy • Under dosing
Preparing the device for administration	• Priming/testing the device prior to administration	• Delay of therapy • Missed dose • Under dosing
Inserting the nozzle into the nostril	• Not inserting in the nostril correctly or not at all	• Missed dose • Under dosing • Delay of therapy
Pressing the plunger to release the dose into the nose	• Not pressing the plunger	• Missed dose
Waiting 2 to 3 minutes before giving the second dose, if the person doesn't respond	• Not waiting long enough between doses	• The safety profile of Naloxone indicates that there is no particular safety concern when administered earlier than 2-3 minutes after the first dose.
Calling 911	• Not calling emergency medical services	• Delay of therapy from medical services
Moving to recovery position after administering dose	• Moving the user to improper recovery position	• Difficulties of breathing • Difficulties of airway protection from obstruction

The sponsor states that the critical tasks identified are:

- Inserting the nozzle into the nostril and
- Pressing the plunger to release the dose into the nose

To justify only identifying only two critical tasks the sponsor states:

There were additional tasks that resulted in a missed dose, which could be considered critical tasks. However, all the tasks involving a missed dose (for e.g., opening the blister to take device, preparing the device for administration) lead to the above two critical tasks. Therefore, by testing the above two critical tasks all the other tasks involving missed dose will be covered.

Reviewer Note

While I understand the thought process that the sponsor states with regards to critical task choice, this is not an acceptable way to define critical tasks in accordance with the FDA Guidance: Applying Human Factors and Usability Engineering to Medical Devices (<https://www.fda.gov/media/80481/download>). The sponsor needs to identify all critical tasks that could result in serious harm to the patient. It is important that all critical tasks are designated as critical tasks, to ensure that failures or difficulties are noted; for example this should include tasks such as open up blister pack and administer second dose if needed. I will leave this up to DMEPA as CDER is the lead center.

Reviewer Note to DMEPA Reviewers -(sent to CDER/OSE/DMEPA reviewer team Cameron Johnson and Otto Townsend on 10/4/2019):

The sponsor is proposing to only include two critical tasks:

- Inserting the nozzle into the nostril and
- Pressing the plunger to release the dose into the nose

They acknowledge that there are other tasks that could lead to the user not providing the full dose but are not including them as critical tasks in the HF validation study:

There were additional tasks that resulted in a missed dose, which could be considered critical tasks. However, all the tasks involving a missed dose (for e.g., opening the blister to take device, preparing the device for administration) lead to the above two critical tasks. Therefore, by testing the above two critical tasks all the other tasks involving missed dose will be covered.

We believe that such tasks should be included in the HF validation study, as it is important to monitor difficulties, close calls, etc.; additionally, it is unclear how the sponsor is identifying critical tasks, it only appears to be based on the a missed dose or under dose.

Update 10/9/2019:

A teleconference was held on 10/9/2019 with CDER/DMEPA . They stated that they had already evaluated the protocol and had recommended that a new HF study be completed. They had already evaluated the new HF protocol under IND134954 and had ensured me that although the sponsor is not evaluated the tasks such as “opening the blister pack” as critical tasks, there is observation of difficulties of opening, or other similar tasks, to ensure they are completed. This mitigated my concerns that were noted above. I defer the remaining portion of the HF review to the CDER/DMEPA.

The sponsor provides the summary results of the human factors testing:

PRIMARY ENDPOINTS			
Successful Tasks	Actions		Comments
	Potential Actions	Observed Actions	
<i>Inserting the device nozzle into a nostril</i>	Inserting the nozzle into the nostril Putting the nozzle near the nostril (not in the nostril) Other	30 out of 31 test subjects inserted the nozzle into the nostril correctly for the first dose. One test subject held the device upside down when attempting to give the first dose. All test subjects inserted the nozzle in the nostril correctly for the second dose.	The terms nasal spray and nostril were understood. The shape of the device makes the actions intuitive. One test subject held the device upside down and inserted the plunger in the nostril. She paused, knowing something was wrong, but seemed confused (subject ID (b) (6) 67 years of age, low-literacy population). When she appeared to be unable to figure out her error, the moderator told her she was holding the device incorrectly. She then completed the task correctly. She correctly administered the second dose.
<i>Pressing the plunger to release a full dose into the nose</i>	Pressing the plunger to release a full dose Partially pressing the plunger Not pressing the plunger	30 out of 31 test subjects pressed the plunger to release a full dose for the first dose. One test subject held the device upside down when attempting to give the first dose. All test subjects pressed the plunger to release a full dose for the second dose.	Test subject ID (b) (6) who held the device upside down held the plunger near the nostril and was unable to press the <i>plunger</i> (since she was actually pushing on the nozzle). When she was unable to depress the <i>plunger</i> and was not able to figure out her error, the moderator told her she was holding the device incorrectly. She then completed the task correctly. She pressed the plunger correctly for the second dose.
SECONDARY ENDPOINTS			
Successful Tasks	Actions		Comments
	Potential Actions	Observed Actions	
<i>Identifying the overdose (checking for response)</i>	Checking for a response (talking to the patient, observation, etc.) Not checking	27 out of 31 test subjects checked to see if the "patient" was responsive. 4 test subjects did not make any noticeable attempt to check the patient.	The 4 test subjects who did not check the mannequin for signs of an overdose assumed it was an overdose situation based on the initial instructions from the moderator. The moderator read an introductory statement: <i>You will be asked to enter the room. You will find the drug to administer next to the mannequin. This is the person who has overdosed.</i> Those who checked for signs of an overdose were more literal in their interpretation of: <i>Do not assume anything. Act as if you came across this person and suspect an opioid overdose situation.</i>

SECONDARY ENDPOINTS			
Successful Tasks	Actions		Comments
	Potential Actions	Observed Actions	
Calling 911	Pretending to call 911 No mention that they would call 911	30 out of 31 test subjects indicated they would call 911.	Test subject ID (b) (6) did not indicate she would contact 911 during the simulation. She replied in the affirmative when asked the question: <i>After the drug is given, is it still necessary to get emergency help by calling 911?</i> When asked why she did not mention calling 911 in the simulation, she said she was focused on her tasks and would call 911 if it "was a real person."
Waiting 2 to 3 minutes to assess the effectiveness of the first dose	Waiting 2 to 3 minutes Waiting longer than 2 to 3 minutes Waiting less than 2 to 3 minutes	25 out of 31 test subjects waited 2 to 3 minutes before administering the second dose. When the test subject began to time the wait period, the test moderator said to assume 2 to 3 minutes had passed.	Test subject ID (b) (6) immediately gave the second dose. She did not see the instruction to wait and saw two devices, so she used them both. She assumed one device per nostril. Test subject ID (b) (6) tried to use the first device a second time. Realizing his error, he immediately used the second device. He misread the word "either" and thought it was "each" nostril. Test subjects ID (b) (6) assumed time had passed even though they were not told that the time had passed by the moderator. Test subject ID (b) (6) immediately gave the second dose because she thought she did the first dose incorrectly. (The first dose was given correctly.) Test subject ID (b) (6) waited one minute and proceeded. He was not told by the moderator to assume 2 to 3 minutes had passed. Four of these test subjects were drawn from the low-literacy population.

SECONDARY ENDPOINTS			
Successful Tasks	Actions		Comments
	Potential Actions	Observed Actions	
<i>Moving to a recovery position after administering the dose</i>	Moving the mannequin into the described recovery position	10 subjects (b) (6) put the mannequin in the recovery position after giving the first dose and after giving the second dose.	Test subject ID (b) (6) did not move the mannequin into a recovery position because she was "checking for other signs, focused on calling 911, and did not see the diagram on the box."
	Moving the mannequin into a different recovery position	1 subject (b) (6) put the mannequin in the recovery position after giving the first dose and left it in the recovery position for the second dose.	Test subject ID (b) (6) would not move a person in case the person had broken bones.
	Not moving the mannequin into a recovery position	1 subject (b) (6) moved the mannequin into the recovery position after the first dose but left the mannequin on its back after giving the second dose.	Test subject ID (b) (6) did not read the directions at any point in the simulation.
		6 subjects (b) (6) put the mannequin in the recovery position only after administering both doses.	Test subject ID (b) (6) said he had no first aid experience. Later when he noticed the picture, he understood what should have been done.
		9 subjects (b) (6) left the mannequin on its back after both doses.	Test subjects ID (b) (6) said they did not notice the instructions to move the patient to a recovery position.
		4 subjects (b) (6) made a decision about a recovery position, but did not use the one as prescribed in the directions.	Test subject ID (b) (6) was given a scenario of "mannequin face down." After the first dose was given, he rolled the mannequin onto its side as part of the dosing process. For the second dose, he rolled the mannequin onto its back and did not adjust it after the second dose.
			Test subject ID (b) (6) would sit the person upright.
			Test subject ID (b) (6) would prop the person up so they would not swallow their tongue.
			Test subject ID (b) (6) would wait for help to move the person.
<i>Administering another dose using a new unit (if needed)</i>	Administering another new dose	30 out of 31 test subjects administered a second dose.	Test subject ID (b) (6) did not give another new dose. He did not see the second device in the box.
	Not administering another new dose		

Reviewer Note:

One user out of 31 failed to administer the dose properly. The sponsor states this was due to confusion; however, the identical (b) (6) device is used with the approved Narcan drug product, with the same use steps. Given that there is an approved product with the same use steps, I believe that a single user failing does not raise any large concerns. This being said, I defer to DMEPA if use tasks such as "Opening the Blister Pack" or "Administering another dose if needed"

Human Factors Validation Recommendation:

The Human Factors Validation information is deferred to DMEPA. One comment was previously sent to CDER/OSE/DMEPA for their review.

10.FACILITIES & QUALITY SYSTEMS

10.1. Facility Inspection Report Review

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

Reviewer Note:

See Section 4 where the facility information is discussed, specifically Section 4.3, where it was discussed the final device manufacturer was changed mid-review.

Firm Name:	West-Ward Columbus Inc.
Address:	1809 Wilson Road (b) (4) Columbus, Ohio, USA
FEI:	1510690 (DUNS #058839929)
Responsibilities:	(b) (4) Product manufacturing, packaging, and labeling will be performed at the (b) (4) building. Drug product microbiological testing may also be performed at the (b) (4) building as an alternate testing facility to (b) (4).

Facility Regulatory History Review	
Firm Name:	West-Ward Columbus Inc.
Address & FEI:	1809 Wilson Road (b) (4), Columbus, Ohio, USA 1510690 (DUNS #058839929)
Responsibilities:	(b) (4) Product manufacturing, packaging, and labeling will be performed (b) (4). Drug product microbiological testing may also be performed at (b) (4) an alternate testing facility to (b) (4).
Site Inspection Recommendation:	Inspection Not Yet Completed as of 10/4/2019 – PAI being requested.

10.2. Quality Systems Documentation Review

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

Reviewer Note:

The sponsor changed the device manufacturer mid-review; therefore the device manufacturer quality systems information that was provided in the original review for Insys is no longer applicable to the new device manufacturer West Ward Columbus Inc (WWCI).

All quality system information will be requested given the manufacturer site change. **See MC comments.**

10.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts and the Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product. The information below corresponds to the manufacturing of the product prior to the manufacturer change.

Naloxone Nasal Spray



Reviewer Comments

It is unclear if any of this information has changed because of the manufacturer change. The sponsor should clarify if this information has changed. In 3.2.P.3.1 (Seq00015), the sponsor states that WWCI responsibilities are the following:

(b) (4)

Product manufacturing, packaging, and labeling will be performed (b) (4).

Drug product microbiological testing may also be performed at (b) (4) *an alternate testing facility* (b) (4).

It is unclear if all of the QS information provided in the original NDA submission is the same for the new site.

Update 12/16/2019:

The sponsor has provided updated information for the manufacturing site change to complete a QS review. See below:

Device Manufacturing Process Conclusion

The Sponsor provided adequate information for the summary of the manufacturing process / production flow.

☒ Yes

☐ No

10.2.2. 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 –

[Review Instructions](#)

☐ Stream-line Both ([no streamlined approach](#))

Reviewer Note:

As stated above, it is unclear if any of this information has changed because of the manufacturer change. The sponsor should clarify if this information has changed. In 3.2.P.3.1 (Seq00015), the sponsor states that WWCI responsibilities are the following:

(b) (4)

Product manufacturing, packaging, and labeling will be performed (b) (4).

Drug product microbiological testing may also be performed at (b) (4) an alternate testing facility (b) (4).

It is unclear if all of the QS information provided in the original NDA submission is the same for the new site.

Update 12/16/2019:

The sponsor has provided updated information in the MC IR response for the manufacturing site change to complete a QS review. See below

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Hikma	Reviewer Discussion – The sponsor states: <i>Hikma acknowledges the Agency's request to provide a summary of our management structure. Hikma's management structure with executive responsibility is required to ensure that the quality policy is understood, implemented and maintained at all levels of the company, and plant organizations. Hikma's company organization, esponsibilities/authority, resources, management representative, quality management review (Quality Committee and Quality Governance Boards), Quality Planning,</i>
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		and Quality System processes are governed through our Quality Manual and Quality Control Unit (QCU) internal procedures. The description appears appropriate.
21 CFR 820.30 Summary of Design Controls	Firm(s): Hikma	Reviewer Discussion – The sponsor states: <i>Hikma acknowledges the Agency’ s request to provide a summary of our design control system for the device constituent part and combination product. Design controls are a structured method of ensuring that the device and drug function together as required. A design control process requires the following steps, which are separated into three distinct phases:</i> Phase 1: Development and Design: • <i>Product Identification</i> • <i>Design Planning</i> • <i>Design Input</i> • <i>Design Output</i> • <i>Design Verification</i> • <i>Design Validation</i> Phase 2: Design Transfer: • <i>Design Transfer</i> • <i>Process Validation</i> Phase 3: Lifecycle Management: • <i>Design Changes</i> <i>Design Control incorporates periodic Design Reviews at designated stages within the design control process (i. e. at the end of each design phase or as applicable). The Design Review consists of a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, evaluation the capability of the design to meet those requirements and identify potential design problems early in the development process.</i> <i>A Design History File (DHF) is maintained for each combination product. The DHF is a compilation of records which describes the design history of the medical device and is subjected for design reviews. Hikma will maintain the DHF for portions of the device/combination product, which are under Hikma control with references to the</i>

		<i>specific contract manufacturer(s) responsible for their parts of the DHF (e.g. (b) (4) .</i> <i>All design control process steps are described in the design control internal procedure for development and for transfer and lifecycle, while design changes are controlled by the change control internal procedure. Design controls ensure that specified design requirements are met including user needs and the intended use of the finished product. The design control process is defined in three distinct phases: Design and Development, Design Transfer, and Lifecycle management and commercial manufacture. These phases are aligned with the stages of drug process validation. Hikma’ s internal procedures are available for review on site.</i> The description appears appropriate.
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Hikma	Reviewer Discussion – The sponsor states: <i>Hikma acknowledges the Agency’ s request to provide a summary of our purchasing control system for the device constituent part for use in this combination product. Purchasing control processes are established and maintained to ensure that all purchased or otherwise received product and services conform to specific approved specifications and requirements. Suppliers are selected and evaluated as a part of the company’ s supplier management program. This evaluation comprehensively assesses the supplier’ s financial status, business operations, regulatory/cGMP compliance as well as safety and social performance. Supplier performance data for purchased or otherwise received product is managed through purchasing agreements, quality agreements, and testing specifications. These agreements contain a requirement that the supplier will provide prior notice of changes. Hikma’ s purchasing control processes are described in the Hikma’ s internal procedures. Hikma’ s internal procedures are available for review on site.</i> The description appears appropriate.
21 CFR 820.100 Summary of Corrective and	Firm(s): Hikma	Reviewer Discussion – Reviewed in Section 12.2.3.

Preventive Actions		<i>Hikma acknowledges the Agency' s request to provide a summary of our corrective and preventive actions (CAPA) system. Hikma' s CAPA process is described in the CAPA internal procedures. Hikma' s CAPA is the mechanism that identifies, implements, and verifies effectiveness of actions to correct the root cause of deviations, trends, complaints and other nonconformance's. The device component, assembly and design are considered during root cause analysis during investigations to identify existing and potential cause of nonconformances. The CAPA process also includes preventative measures to prevent occurrence of potential issues. Hikma' s internal procedures are available for review on site.</i> The description appears appropriate; however, additional details are necessary. See deficiencies to be sent to sponsor.
21 CFR 820.170 Summary of Installation	Firm(s): N/A	Reviewer Discussion – This is N/A
21 CFR 820.200 Summary Servicing	Firm(s): N/A	Reviewer Discussion – This is N/A

Reviewer Comments

The quality systems information from a high level appears appropriate. I defer specific review of the 21 CFR 820 requirements specific to the device manufacturer such as acceptance activities, non-conforming product handling, labeling, records, etc. until after the preapproval inspection is conducted and feedback is received from the ORA inspector.

GMP Compliance Summary Conclusion

The Sponsor provided adequate summary information about the GMP compliance activities	☐ Yes	☐ No
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10.2.3. Corrective and Preventive Action Review

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.	No
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.	No
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	No

Investigations into the cause of nonconformities relating to product, processes, and the quality system	No
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	No
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	No
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	No
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	No
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	No
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	No
Requires documentation of all CAPA activities	No

Reviewer Comments

The sponsor states the following regarding their CAPA procedures:

Hikma acknowledges the Agency's request to provide a summary of our corrective and preventive actions (CAPA) system. Hikma's CAPA process is described in the CAPA internal procedures. Hikma's CAPA is the mechanism that identifies, implements, and verifies effectiveness of actions to correct the root cause of deviations, trends, complaints and other nonconformance's. The device component, assembly and design are considered during root cause analysis during investigations to identify existing and potential cause of nonconformances. The CAPA process also includes preventative measures to prevent occurrence of potential issues. Hikma's internal procedures are available for review on site.

Hikma should provide the CAPA procedures for our review. **See CR deficiencies to sponsor.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.

☐ Yes

☐ No

10.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents. This is provided Seq000.3.2.P.5.1

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)
Spray Actuation Content	Design verification, lot release testing. Sponsor should provide summary of how they are controlled for with any other acceptance or in-process controls.	No
Spray Pattern	Design verification, lot release testing. Sponsor should provide summary of how they are controlled for with any other acceptance or in-process controls.	No
Droplet Size Distribution	Design verification, lot release testing. Sponsor should provide summary of how they are controlled for with any other acceptance or in-process controls.	No
Spray Content Uniformity	Design verification, lot release testing. Sponsor should provide summary of how they are controlled for with any other acceptance or in-process controls.	No
Plume Geometry	Design verification. Sponsor should provide summary of how they are controlled for with any other acceptance or in-process controls.	No
Actuation Force	Design verification. Sponsor should provide summary of how they are controlled for with any other acceptance or in-process controls.	No

Reviewer Comments

The Sponsor provides a general control strategy for the device; i.e. design verification, purchasing controls and incoming inspections, but they do not provide a description of how these strategies particularly ensure that the essential performance are controlled through incoming acceptance, in-process control, and/or release testing activities. This should be provided. **See CR deficiencies.**

Update 12/18/2020:

The sponsor responded to the CR deficiencies in their re-submission.

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

10.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Reviewer Recommendation:

The facilities and QS information is adequate.

11. INFORMATION REQUEST: MIDCYCLE

A. Midcycle Deficiencies

Deficiencies to NDA Holder (NDA 212045) – Response Received October 18, 2019

1. In document: container-closure-system, you provide reference to the device specific dFMEA that is completed by the device constituent manufacturer, (b) (4). However, this does not take into account the drug constituent of the combination product. Therefore, the hazards and risk levels that are currently corresponding to specific failure modes may not be reflective of the combination product hazards and corresponding risks levels, and may require additional risk mitigation activities. As requested in the Agency's previous Type B comments, meeting date August 29, 2018, provide a device design related risk analysis, in accordance with ISO 14971, that is inclusive of the risks/risk levels associated with the full combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your combination product, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device.

Sponsor Response:

Hikma acknowledges the Agency's request for a design related risk assessment in accordance with ISO 14971 that is inclusive of the risks/risk levels associated with the full combination product. Our risk analysis will include all identified risks, potential hazards that are apparent to our combination product, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device.

Timeline: Target date for response submission is April 30, 2020

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

2. Confirm that the final finished combination product has been clinically validated in either a pivotal clinical trial and/or bioequivalence study. If so, provide a reference to this study information. If there have been any changes to the device design used in the pivotal clinical trial and/or bioequivalence study, describe the differences (design and manufacturing) and provide justification for why the differences would not impact the performance requirements that were validated in the clinical study. It may be necessary for you to provide bridging information if the device used in the clinical study differs significantly from the to-be-marketed device.

Sponsor Response:

Hikma acknowledges the Agency's request to provide a reference to the study information confirming that the final finished combination product has been clinically validated in either a pivotal clinical trial and/or bioequivalence study. This information has been provided in Module 3.2.P.2.4. Additionally, Hikma would like to clarify that there have been no changes to the device design used in the pivotal clinical trial and/or bioequivalence study as confirmed in section 4.2 of Module 3.2.P.2.4 "containerclosure-system."

Timeline: Information requested has been submitted within this amendment.

FDA Response:

The sponsor has clarified that the device constituent has been clinically validated in the pivotal clinical trial/BE study. This is adequate.

3. You provide shelf-life testing using stability lots of the to-be-marketed device in 3.2.P.8. This testing includes device performance testing for spray actuation content, spray content uniformity, spray pattern and droplet size

distribution. The stability lots include multiple different storage conditions including accelerated aging conditions. It is noted that in document “stability-summary” that you have provided real time aging to 12 months and accelerated aging for 6 months (at 40 °C) . State the equivalent real time age of the accelerated aged lots (6 months at 40°C) and if it is equivalent to the proposed 24 month shelf life.

Sponsor Response:

Hikma acknowledges the Agency’ s request to state the equivalent real time age of the accelerated aged lots and if it is equivalent to the proposed 24 month shelf life. Results for all test parameters included in the Naloxone Nasal Spray stability program are in conformance with the acceptance criteria for all primary and supportive stability studies at refrigerated, long term and accelerated storage conditions, in all orientations and all strengths. Based ICH Q1E, 6 months of accelerated and 12 months of real-time stability data have been provided with little to no variability; therefore, a shelf life of 24 months is supported for the product. Additionally, stability data will be provided at accelerated conditions through 24 months for the primary lots manufactured at Insys to confirm the performance tests of the device support a 24 month expiry.

Timeline: The target date for submission of the 24 months stability data of the primary batches manufactured at Insys to confirm the proposed expiry of 24 months is February 29, 2020.

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

4. Clarify if there are any design or manufacturing differences between the device constituents from the stability batches to the to-be-marketed batches. For every difference identified, provide justification that the differences do not impact the device essential performance requirements. If there are any changes that could affect the essential performance requirements of the device, provide additional bridging information.

Sponsor Response:

Hikma acknowledges the question to clarify if there are any design or manufacturing differences between the device constituents from the stability batches to the to-be-marketed batches. For commercial marketing, Hikma intends to keep the design specifications of the device and device suppliers identical to that submitted by Insys for stability/exhibit batches. Based on this, please note that no changes to the device constituents will be made from the stability batches to the to-be-marketed batches.

Timeline: Information requested has been submitted within this amendment.

FDA Response:

The sponsor has clarified that the commercial device constituent will contain the identical design specifications and will use the same suppliers. This is adequate

5. You do not define an actuation force specification or include it in your release testing (3.2.P.5.1) of the final finished device. It is noted in document: container-closure-system, that you state that Actuation force performance is approximately (b) (4), but it is unclear if you have identified a specification that is appropriate for the users of your device; i.e. adults and pediatrics, that your device can reliably meet that specification over shelf-

life or that you will manufacturer final finished devices that meet this specification. If the actuation force is too high, a user will be unable to actuate the device. Therefore, Provide the following:

- a. Define a specification for actuation force and add it to your release testing (3.2.P.5.1).. .
- b. Provide the test method that was used to verify device actuation force.
- c. Provide an evaluation of your current testing against the actuation force specification to support the acceptability of your testing.
- d. In Table 7, you list the accelerated aging parameters that were used for specific lots; i.e. 6 months 25°C/60% RH and 6 months 40°C/75% RH. State the equivalent real time age of these accelerated aged lots and if this is equivalent to the proposed 24 month shelf life to support your proposed shelf life.
- e. State how you validated the actuation force specification to demonstrate that the upper specification in part a is appropriate for the intended users of your product.
- f. You have not verified actuation force as a part of your transportation study in test report Report.CH.0142, to demonstrate that the shipping conditions would affect the actuation force of the device. Provide testing verifying the actuation force after shipping.

Sponsor Response:

Hikma acknowledges the FDA comment regarding an Actuation Force specification for release testing and commits to implementing an Actuation Force test method to verify device actuation force at release and over shelf-life. Hikma will submit the outcome of Actuation a Force evaluation, and propose any required test methodology and specification.

Timeline: Target date for response submission is June 30, 2020

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

6. You do not define a plume geometry specification or include it as part of release testing (3.2.P.5.1) of your final finished device. While you provided plume geometry testing in document: container-closure-system, to demonstrate consistency, it does not appear that you have defined a specification for plume geometry that is needed to ensure that the necessary clinical treatment/effect is delivered appropriately, that your device can reliably meet the specification over shelf life or that you will manufacture final finished devices that meeting this specification. Therefore, provide the following:
 - a. Define a specification for plume geometry and include plume geometry to your release testing (3.2.P.5.1).
 - b. Provide the test method that was used to verify plume geometry.
 - c. Provide an evaluation of your current testing against the plume geometry specification to support the acceptability of your testing.
 - d. In Table 2, you list the accelerated aging parameters that were used for specific lots; i.e. 6 months 25°C/60% RH and 6 months 40°C/75% RH. State the equivalent real time age of these accelerated aged lots, and if this is equivalent to the proposed 24 month shelf life to support your proposed shelf life.
 - e. You have not verified product plume geometry as a part of your transportation study in test report Report.CH.0142, to demonstrate that the shipping conditions would affect the plume geometry of the drug exiting the device. Provide testing verifying plume geometry after shipping.

Sponsor Response:

Hikma acknowledges the FDA comment regarding plume geometry and commits to continued monitoring of plume geometry data for characterization during Insys exhibit batch stability studies and future exhibit batch analysis using analytical procedure TM.CH.0177 (*Plume Geometry Determination for Nasal Sprays*, validated as per Report.CH.0145). In general, plume

geometry is a characterization test that is not required with commercialization as stated in the current *Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* section III.F.2.h, “plume geometry typically should be established during the characterization of the product and is not necessarily tested routinely thereafter” .

Hikma further commits to provide an evaluation and summary of the plume geometry data collected for Insys exhibit batch stability as well as future exhibit batch data manufactured at West-Ward Columbus Inc.

Timeline: Target date for response submission is June 30, 2020.

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

7. In your product specification sheet for release/shelf life testing in 3.2.P.5.1, you list the droplet size distribution (DSD) and spray pattern of the product at (b) (4) from the outlet of the nasal spray device; however, it is noted in your design verification testing you provided testing of DSD and spray pattern at (b) (4). It appears that (b) (4) is recorded only for informational purposes. Explain why there is no acceptance criteria around DSD and spray pattern at (b) (4) and why DSD and spray pattern does not need to be controlled for during release and stability testing. This discussion should include other controls that are used to ensure that DSD and spray pattern is met at release.

Sponsor Response:

Hikma acknowledges the FDA comment regarding the product specification sheet and commits to adding acceptance criteria to the proposed release/shelf life specification for droplet size distribution and spray pattern a both (b) (4) with the future exhibit batch data.

Timeline: Target date for response submission is June 30, 2020 manufactured at West-Ward Columbus Inc.

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

8. Address the followings regarding your Spray Actuation Content specification:
- Your specification for Spray Actuation Content is not aligned with and is wider in terms of the allowable error from the nominal delivery volume, than the recommended specification for pump delivery in The FDA Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (<https://www.fda.gov/media/70857/download>). We recommend that you alter your specification to be aligned with the referenced guidance. Alternatively, justify the clinical relevance of the Spray Actuation Content specification. This justification should rely on the results of your clinical validation testing.
 - You only propose to test (b) (4) units as a part of the Spray Actuation Content design verification and release testing. It is unclear, how you have determined that a sample size of (b) (4) for design verification and at release, achieves an appropriate level of confidence/reliability for Spray Actuation Content of your product, given the intended use of your product. Provide the following
 - Justify the relevance of testing (b) (4) devices as a part of lot release testing.

- ii. With regards, to your spray actuation content verification reliability/confidence, please note that we expect a 99.9% reliability/95% confidence per our previous Type B comments. Please see question 10.

Sponsor Response:

- a. We acknowledge that Spray Actuation Content (Pump Delivery) is not aligned with the reference guidance. We will review relevant release and verification data as well as acceptance testing for pump delivery on incoming pumps and make appropriate changes to acceptance criteria on the drug specification.
- b. Hikma will review the sample size utilized for design verification and at release to ensure it is appropriate to ensure the level of confidence/reliability for Spray Actuation Content of our product provides the following:
 - i) Justification of sample size for lot release.
 - ii) Sample size adequate to demonstrate spray actuation content verification to the appropriate level reliability/confidence.

Timeline: Target date for response submission is June 30, 2020

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

9. In document "Report.CH.0144", you state that you conducted a fault tree analysis (FTA) with a top-level failure mode of "Device fails to actuate", using your manufacturing/assembly information and failure rate information from your device component supplier dFMEA to support your device reliability. We do not believe that the current FTA supports a 99.99% reliability with 95% confidence for failure to deliver the full intended dose.

Address the following comments regarding your FTA:

- a. You state that your top level failure mode for your device within the FTA is "device fails to actuate". As stated in our previous Type B comments that you reference, we recommend that the top level failure mode be "Failure to deliver the full intended dose", as device failing to actuate would be considered a sub-failure mode under failure to deliver the dose.
- b. You do not appear to be considering multiple failure modes that could occur; i.e. failure of one and/or more of the critical components or one of the critical dimensions of the components. This should be included in your FTA.
- c. You are currently referencing the failure modes identified in the device component supplier dFMEA that would affect the device actuator and would result in no dose. This dFMEA includes the manufacturer's approximation for probability associated with the following defects:
 - Cannula falls off spray pin
 - Cannula moves during plunger piercing
 - Cannula pierces plunger out of center axis
 - Cannula does not pierce plunger fully.

While the supplied dFMEA provides an approximation of an individual failure rate, the individual failure modes should be incorporated into your FTA, with supporting empirical data referenced to support the failure rate of the top level failure mode. We note that you have supplied incoming component testing and results in test report "Report.CH.0144" where you have characterized the upper and lower specifications for the actuation, holder, stopper and vial, it is unclear how this testing corresponds to the individual failure modes (defined in the dFMEA) affecting the top level failure mode in your FTA. The links between the possible device failure modes that control for the top level failure mode and your process

controls to control the components critical to these failure modes are needed to understand how you, as the final to be marketed device manufacturer, are controlling for the top level failure mode to achieve and maintain a 99.99% reliability.

Given that you are proposing to reference a DMF nasal spray device where you may have limited knowledge of device design and/or manufacturing controls, you should define the tolerances of the device components taking into account the individual components and their use in conjunction with associated components of the device that would result in the top level failure mode, then reference your incoming/assembly component testing and results for the device components that could affect the top level failure mode of “failure to deliver the full intended dose” to support the overall reliability in your FTA. Please provide this in an updated FTA, with the summary data that was collected to support the overall reliability.

- d. Based on Table 3 and 4 in document “Report.CH.0144”, it does not appear that you are considering for (b) (4) cannula, spray pin, or nozzle in your inspections/in process inspections. Since these appear to be failure modes identified in the component supplier FTA, these should be considered in the FTA for device reliability.
- e. On 9/20/2019, you provided responses to FDA questions stating that “Hikma wishes to inform the Agency that commercial manufacturing will be moved to West-Ward Columbus Inc. (WWCI) in Columbus, Ohio”. You have completed your FTA using the device control processes at Insys, not WWCI. Please provide edits to your FTA based on your proposed device control processes at WWCI to demonstrate that your current processes allow for your product to meet a 99.99% reliability for “Failure to deliver the full intended dose”.

Sponsor Response:

- A. We acknowledge that “Failure to deliver the full intended dose” needs to be addressed in the fault tree analysis (FTA). Hikma will make appropriate revisions to the FTA.
- B. Hikma recognizes that the FTA does not include multiple failure modes that could occur. We will revise the FTA accordingly.
- C. Hikma will revise the FTA to incorporate individual failure modes. Empirical data will be referenced to support the failure rate of the top level failure mode. We will provide an updated FTA, with the summary data that was collected to support the overall reliability.
- D. Hikma will evaluate whether (b) (4) cannula, spray pin, or nozzle need to be included in our inspections/in process inspections. We will also evaluate the FTA for device reliability and update as appropriate.
- E. Hikma will update the FTA using device control processes at WWCI to demonstrate that our product meets appropriate reliability for “Failure to deliver the full intended dose” .

Timeline: Target date for response submission with batch release and three-month accelerated stability (40°C/75%RH) results is June 30, 2020.

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

10. To support verification of your system level reliability you provide Spray Actuation Content performance testing in document: "Report.CH.0144". You state "*Insys tested at least 480 devices each from two lots of combination product packaged in 20 shippers each to verify reliability*". Address the following comments regarding your protocol:
- Explain the statistical methodology behind the inclusion of 480 devices from two lots and how this equates to a 99.99% reliability with 95% confidence for spray actuation content.
 - You do not provide testing of the device essential performance requirements (EPRs) to a 99.99% reliability with 95% confidence, as recommended in the previous Type B comments. As stated in our previous Type B comments, the Agency considers Spray Actuation Content/Dose Accuracy, Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force to be the EPRs for your device type, as these performance requirements are necessary for your device constituent to safely and effectively achieve the combination product's intended use; therefore we recommend that you provide verification testing to support a 99.99% reliability with 95% confidence for these specific EPRs.
 - It is noted that you state that one lot was the (b) (4)% alcohol product and the other was the to-be-marketed 20% alcohol product. It is unclear how the use of the (b) (4)% drug product is applicable to support the reliability of the 20% product. While the device may be the same, the use of the different drug product could potentially influence the drug spray characteristics. Provide justification why using the (b) (4)% drug product would not impact the drug spray characteristics.
 - You state that all devices were exposed to accelerated aging conditions (40°C 75%RH for at least 6 months). State the equivalent real time age of these accelerated aged lots, and if this is equivalent to the proposed 24 month shelf life to support your proposed shelf life. Note that we expect that the devices tested in the reliability study will support the shelf life of the product.

Sponsor Response:

- Hikma acknowledges the Agency's request for rationale for statistical sample size. We will provide rationale in our updated reliability for combination product manufactured at WWCI.
- Additionally, the updated reliability testing will include verification testing of device essential performance requirements.
- Hikma acknowledges the FDA request to justify why using the (b) (4)% alcohol product would not impact the drug spray characteristics when compared to the 20% alcohol product. Hydroalcoholic formulations containing 20% and (b) (4)% alcohol were separately manufactured and individually studied for clinical studies only. Equal number of lots for the 20% and (b) (4) alcohol formulation were manufactured for registration/ clinical studies resulting in both formulations meeting the pre-determined acceptance criteria for (b) (4) solution and finished product (assembled device). Based on overall clinical and non-clinical data, only the formulation with 20% alcohol was selected for commercial marketing.

Hikma acknowledges that the (b) (4) % alcohol formulation may have slightly different spray characteristics compared to that of the 20% alcohol formulation due to minor differences in (b) (4) solution properties including viscosity, specific gravity, and density. However, Hikma does not intend to market the formulation with (b) (4) % alcohol; formulation with 20% alcohol is selected for commercial marketing based on its individual merit noted by the successful production of registration/ clinical batches, acceptable results from (b) (4) and finished product testing, and acceptable clinical studies. The (b) (4) alcohol product is only used to support robustness of the device constituents. Hikma commits to only making the 20% alcohol product for the site transfer batches and commercially.

- d. Hikma acknowledges the Agency' s request to state the equivalent real time age of the accelerated aged lots and if it is equivalent to the proposed 24 month shelf life. Results for all test parameters included in the Naloxone Nasal Spray stability program are in conformance with the acceptance criteria for all primary and supportive stability studies at refrigerated, long term and accelerated storage conditions, in all orientations and all strengths. Based ICH Q1E, 6 months of accelerated and 12 months of real-time stability data have been provided with little to no variability; therefore, a shelf life of 24 months is supported for the product. Additionally, stability data will be provided at accelerated conditions through 24 months for the exhibit lots manufactured at Insys to confirm the performance tests of the device support a 24 month expiry.

Timeline: Target date for response submission with batch release and three-month accelerated stability (40°C/75%RH) results to support subparts a and b is June 30, 2020. Response 21c is submitted within this amendment. The target date for submission of the stability data associated with subpart d is February 29, 2020.

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

Specific to part c, the sponsor states that the (b) (4) % alcohol formulation was use to support the “robustness of the device constituents” for the purposes of the study. This is not adequate as it does not provide any sort of comparative information of drug product characteristics that would support its use in the reliability study. The sponsor should provide a scientifically sound justification for why both formulations can be used for reliability. **See CR deficiencies.**

11. *To support verification of your system level reliability you provide spray actuation content performance testing in document: “Report.CH.0144”. Address the following questions about your test results:*

- a. You state that 10 devices out of 540 devices exhibited separation between the vial and vial holder. While you state that the devices delivered the proper dose, a user may not understand how to reconnect the vial and vial holder with the device, prior to use in an emergency/high stress use environment. You state that the root cause of the failure was the “*shipping drop test not being performed as per the protocol.*” Provide more details regarding the root cause determination and why this drop testing that resulted in vial/vial holder separation would not occur during a typical use/shipping scenario.

- b. In the Lot 1036107 visual inspection after preconditioning, you state that one device was found to have a loose vial holder (plunger), where the bridges connecting the plunger to the actuator were broken, which was caused by higher impact stress applied during simulated shipping. Given the description that the product contained a loose plunger, it sounds reasonable that if the plunger was to be loose, that it could detach from the device constituent, and could result in device failure. Explain how you came to the conclusion that, *“it was suspected that the loose vial plunger would not affect functionality.”*
- c. Referring to the issues noted above, you state: *“In order to mitigate this kind of damage to the device, shipping procedures will be reviewed further, and additional controls will be added prior to commercial launch if appropriate”*. In both cases above, it appears that the preconditioning used in the reliability verification testing resulted in the potential failure modes noted above. Given these potential failure modes noted, provide additional controls to mitigate the risk of vial and vial holder separation and testing demonstrating that they are effective.

Sponsor Response:

- a. Hikma acknowledges the request to provide more details regarding the root cause determination and why this drop testing that resulted in vial / vial holder separation would not occur during typical use / shipping scenarios. Per Reliability Report CH.0144 (Page 14) submitted by Insys, the root cause of the separated vials and vial holders was that the shipping simulation testing facility reported a deviation in the testing conducted for Sequence #2 and #8 Manual Handling Drop test was conducted at Assurance Level I instead of Assurance Level II as per protocol. For Sequence #2, this resulted in use of drop height of (b) (4) instead of (b) (4) per protocol and for Sequence #8 use of drop height of (b) (4) instead of (b) (4). The damage observed to the 10 devices was traced back to this increased impact stress that was not part of the approved protocol. All of the 10 devices were included in the Spray Actuation Content testing verifying that the damage did not impact functionality of the device as supported by all units testing meeting the Spray Actuation Content acceptance criteria for the lot tested (Minimum test result of (b) (4) generated for all units tested).

Although the root cause is probable based on the Insys conclusion and due to the testing not being repeated by Insys, Hikma commits to re-perform the shipping reliability study with drug product produced at West-Ward Columbus to ensure that all tests are performed per the protocol. Results will be discussed in a shipping study report, which will be submitted to the Agency.

- b. Hikma acknowledges the request to clarify the conclusion that, *“it was suspected that the loose vial plunger would not affect functionality”*. Per Reliability Report CH.0144 (Page 15) submitted by Insys, one device was found to have a loose vial holder (plunger), where the bridges connecting the plunger to the actuator were broken. To support the conclusion that *“it was suspected that the loose vial plunger would not affect functionality”*, Insys tested the impacted device for Spray Actuation Content to demonstrate worst case performance of the device. The testing verified that the loose vial holder did not impact device functionality for the lot tested (Minimum test result of (b) (4) generated for all units tested). Although Hikma agrees that the Insys study supported that device functionality was not impacted by the shipping study, Hikma commits to re-perform the shipping reliability study with drug product produced at West-

Ward Columbus to verify that shipping does not impact device functionality. Results will be discussed in a shipping study report, which will be submitted to the Agency.

- c. Hikma acknowledges the request to review current controls to determine if sufficient to protect the drug product / device combination. As stated in 22a and 22b, Hikma will repeat the reliability study with Hikma produced product / device combination. Hikma will also evaluate the control strategy to determine if additional mitigation is needed to protect the product / device combination during shipping.

Timeline: Target date for response submission is June 30, 2020.

FDA Response:

The sponsor identifies the root cause of the failures that were identified; however they also state that they will repeat the shipping validation study to ensure that the product meets specification after shipping. Since this information, will be re-tested and provided in a future submission. This should be reviewed upon resubmission.

12. On 9/20/2019, you provided responses to FDA questions stating that *“Hikma wishes to inform the Agency that commercial manufacturing will be moved to West-Ward Columbus Inc. (WWCI) in Columbus, Ohio”*. You have completed your device performance/reliability verification testing on product that was manufactured/assembled at Insys, not WWCI. Provide process validation testing to demonstrate that the new processes at WWCI will allow the device to meet its essential performance requirement (EPR) specifications at a 99.99% reliability and 95% confidence: Spray Actuation Content, Dose Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force. The process validation testing may include additional device verification testing at the WWCI manufacturing site to demonstrate that the device EPRs meet their respective specifications and reliability specifications.

Sponsor Response:

Hikma acknowledges the Agency’ s request to perform process validation testing of WWCI produced drug product / devices to demonstrate that the new processes at WWCI will allow the device to meet its essential performance requirement (EPR) specifications. To demonstrate a successful site transfer which will be incorporating the same equipment / processes submitted by Insys, Hikma intends to manufacture and test exhibit/ process validation batches at West-Ward Columbus Inc during Q1 2020. Hikma commits to manufacture three lots and perform routine and supplemental testing for product CQAs and device EPRs during the process validation campaign and to further test on stability. The plan for exhibit/process validation including analytical tests and acceptance criteria will be detailed in a protocol. Observations and results from the exhibit/process validation batches will be summarized in a report, which will be submitted to the Agency to demonstrate WWCI’ s capability to successfully produce and test the drug product / device combination.

Timeline: Target date for response submission is June 30, 2020.

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

13. On 9/20/2019, you provided responses to FDA questions stating that “*Hikma wishes to inform the Agency that commercial manufacturing will be moved to West-Ward Columbus Inc. (WWCI) in Columbus, Ohio*”. It is unclear if all the quality systems responsibilities that were under the purview of Insys have now been transferred to WWCI. List all the responsibilities for WWCI and a summary description of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>). If you plan to implement a drug streamlined approach,:
- a. Provide a summary of your management structure with executive responsibility for those who manage, perform, and assess work affecting quality of the product and related controls to ensure that your quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met, per 21 CFR 820.20.
 - b. Provide a summary of your design control system under 21 CFR 820.30 for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, identify the facility containing the DHF so that the Agency inspection planning activities are appropriately determined.
 - c. Provide a summary of your purchasing control system per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (e.g., sterilization) received at your facility for use in the manufacture of the combination product. The summary should include your evaluation process of your suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes made by the suppliers should be considered in your Purchasing/Supplier agreement as changes to incoming specification that can impact the safety and effectiveness of the final combination product.
 - d. Provide a summary of your corrective and preventive actions (CAPA) system per 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions must be documented under your CAPA System as described in 21 CFR 820.100.

Sponsor Response:

Hikma will be responsible for all the quality systems for this product. Hikma will follow the drug streamlined approach to cGMPs as discussed in sections 4.4(b)(1) of the Combination Products regulations, where Hikma’s base cGMP operations system is the 21 CFR part 210/211 which will include specified provisions within the Quality System regulatory for medical devices (21 CFR 820), including

- 820.20 – Management responsibility

- 820.30 - Design controls
 - 820.50 - Purchasing controls
 - 820.100 - Corrective and preventative action
 - 820.170 - Installation* (*not applicable for this product)
 - 820.200 - Servicing* (*not applicable for this product)
- a. Hikma acknowledges the Agency' s request to provide a summary of our management structure. Hikma' s management structure with executive responsibility is required to ensure that the quality policy is understood, implemented and maintained at all levels of the company, and plant organizations. Hikma' s company organization, responsibilities/authority, resources, management representative, quality management review (Quality Committee and Quality Governance Boards), Quality Planning, and Quality System processes are governed through our Quality Manual and Quality Control Unit (QCU) internal procedures. Hikma' s internal procedures are available for review on site.
- b. Hikma acknowledges the Agency' s request to provide a summary of our design control system for the device constituent part and combination product. Design controls are a structured method of ensuring that the device and drug function together as required. A design control process requires the following steps, which are separated into three distinct phases:

Phase 1: Development and Design:

- Product Identification
- Design Planning
- Design Input
- Design Output
- Design Verification
- Design Validation

Phase 2: Design Transfer:

- Design Transfer
- Process Validation

Phase 3: Lifecycle Management:

- Design Changes

Design Control incorporates periodic Design Reviews at designated stages within the design control process (i.e. at the end of each design phase or as applicable). The Design Review consists of a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, evaluation the capability of the design to meet those requirements and identify potential design problems early in the development process.

A Design History File (DHF) is maintained for each combination product. The DHF is a compilation of records which describes the design history of the medical device and is subjected for design reviews. Hikma will maintain the DHF for portions of the

device/combination product, which are under Hikma control with references to the specific contract manufacturer(s) responsible for their parts of the DHF (e.g. (b)(4)).

All design control process steps are described in the design control internal procedure for development and for transfer and lifecycle, while design changes are controlled by the change control internal procedure. Design controls ensure that specified design requirements are met including user needs and the intended use of the finished product. The design control process is defined in three distinct phases: Design and Development, Design Transfer, and Lifecycle management and commercial manufacture. These phases are aligned with the stages of drug process validation. Hikma's internal procedures are available for review on site.

- c. Hikma acknowledges the Agency's request to provide a summary of our purchasing control system for the device constituent part for use in this combination product. Purchasing control processes are established and maintained to ensure that all purchased or otherwise received product and services conform to specific approved specifications and requirements. Suppliers are selected and evaluated as a part of the company's supplier management program. This evaluation comprehensively assesses the supplier's financial status, business operations, regulatory/cGMP compliance as well as safety and social performance. Supplier performance data for purchased or otherwise received product is managed through purchasing agreements, quality agreements, and testing specifications. These agreements contain a requirement that the supplier will provide prior notice of changes. Hikma's purchasing control processes are described in the Hikma's internal procedures. Hikma's internal procedures are available for review on site.
- d. Hikma acknowledges the Agency's request to provide a summary of our corrective and preventive actions (CAPA) system. Hikma's CAPA process is described in the CAPA internal procedures. Hikma's CAPA is the mechanism that identifies, implements, and verifies effectiveness of actions to correct the root cause of deviations, trends, complaints and other nonconformance's. The device component, assembly and design are considered during root cause analysis during investigations to identify existing and potential cause of nonconformances. The CAPA process also includes preventative measures to prevent occurrence of potential issues. Hikma's internal procedures are available for review on site.

Timeline: Information requested has been submitted within this amendment.

FDA Response:

The sponsor has provided information for how device quality system requirements are being controlled for by the firm. This is reviewed within Section 10.2.2.

- 14. In document: container-closure, you provide a general discussion of your device design controls process, which was previous under the previous manufacturer, Insys. This included discussion of purchasing control and incoming inspections on the device components; however this did not include a discussion of how of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities. As stated previously we consider these to include:

- Spray Pattern
- Spray Content Uniformity
- Droplet Size Distribution
- Plume Geometry
- Actuation Force

Provide a discussion of how the device essential performance requirements listed above are currently adequately controlled for though your control strategy process given the intended use of your product.

Sponsor Response:

Hikma acknowledges the Agency' s request for further details regarding how device essential performance requirements are controlled through our control strategy. We plan to evaluate control strategy as part of the reliability evaluation and will provide details upon completion.

Timeline: Target date for response submission with batch release and three-month accelerated stability (40°C/75%RH) results is June 30, 2020.

FDA Response:

The sponsor did not provide a response to this deficiency and therefore, the response is **not adequate**.

Deficiency to DMF holder (b) (4)

1. We note that you have referenced biocompatibility testing for the device actuator for cytotoxicity, sensitization, and irritation endpoints. These cannot be located within your DMF file. Provide the test protocol and reports used to demonstrate the biocompatibility of the device actuator.

Reviewer Note:

This was requested as a mid-cycle deficiency to the DMF holder. They provided a response stating that the responses were within the paper copy of the DMF. Rather than issuing a comment requesting that they submit the information electronically for ease of review, Venkateswara Pavuluri (OPQ), insisted that this information be reviewed from the paper copy of the DMF. This was requested.

FDA Response:

The biocompatibility information is reviewed within Section 8.4.

12. ORIGINAL RECOMMENDATION

The submission does NOT include adequate information. CDRH recommends that the applicant be issued a CR letter with outstanding deficiencies related to the device constituent (See CR deficiencies in Section 12.1). In addition, a preapproval inspection of the following firm is recommended:

Firm Name:	West-Ward Columbus Inc.
Address:	1809 Wilson Road (b) (4), Columbus, Ohio, USA
FEI:	1510690 (DUNS #058839929)

Resubmission:

A GMP surveillance inspection was conducted on 4/1/2019 through 4/16/2019 at the firm, 1809 Wilson Road (b) (4), Columbus, Ohio, USA, FEI 1510690. This inspection was classified as VAI. The EIR memo was provided and the inspection deemed acceptable. There were no device call outs. No further PAI is necessary.

12.1. CR Deficiencies Issued to the Sponsor & Resubmission Responses from the Sponsor

- 1) In your October 18, 2019 IR response to FDA questions 12 – 25, you provided several responses, with target timelines for completion to June 30, 2020. We request that in a future resubmission that you provide full responses to the questions within this IR that were left unanswered. These include the following questions that were left without a full response in your October 18, 2019 IR response: #12, 14, 16-23.

The following are the FDA's October 18, 2019 IR issues #12, 14, 16-23 and the sponsor's updated responses provided on 12/18/20:

12. In document: container-closure-system, you provide reference to the device specific dFMEA that is completed by the device constituent manufacturer, (b) (4). However, this does not take into account the drug constituent of the combination product. Therefore, the hazards and risk levels that are currently corresponding to specific failure modes may not be reflective of the combination product hazards and corresponding risks levels, and may require additional risk mitigation activities. As requested in the Agency's previous Type B comments, meeting date August 29, 2018, provide a device design related risk analysis, in accordance with ISO 14971, that is inclusive of the risks/risk levels associated with the full combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your combination product, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device.

Sponsor Response:

Hikma acknowledges that the device specific dFMEA that was completed by the device constituent manufacturer, (b) (4) did not take into account the drug constituent of the combination product. As you noted the hazards and risk levels that are currently corresponding to specific failure modes are not reflective of the combination product hazards and corresponding risks levels and may require additional risk mitigation activities.

As requested in the Agency's previous Type B comments, meeting date August 29, 2018, we are providing a device design related risk analysis, in accordance with ISO 14971, that is inclusive of the risks/risk levels associated with the full combination product, TRCOL000323 1927 – Naloxone Nasal Spray Hazard Analysis ISO 14971:2019. The report can be found in Module 3.2.P.7 of this response.

A Risk Management Plan for Naloxone Nasal Spray has been established. This plan details risk analysis that were completed including ISO 14971 Hazard Analysis, User Failure Modes and Effects Analysis (UFMEA), Design Failure Modes and Effects Analysis (DFMEA), and Process Failure Modes and Effects Analysis (PFMEA), Fault Tree Analysis. The risk management plan also includes a Risk Management Report, TRCOL001910, 1927 – Naloxone Nasal Spray, 8mg/spray Risk Management Report, which summarizes risks and risk mitigation and provides a benefits risk analysis that ensures clinical acceptability of any residual risk associated with the device. The report can be found in Module 3.2.P.7 of this response.

FDA Response: They identify the risks and potential hazards in the hazard analysis document. Previously, for the failure mode of cannula does not pierce plunger, it was unclear what are the sub-failure modes of this failure mode; i.e. is it cannula too short/out of spec, plunger material too rigid, etc. They added additional hazards to reflect this. The previous reviewer noted that should be supporting with empirical data for the reliability of each event. This is referenced in the FTA in response to Deficiency #20. The risk management

document includes the hazards, mitigations and the verification of those mitigations via visual inspection, reliability studies, HF studies, etc. **Deficiency resolved.**

14. You provide shelf-life testing using stability lots of the to-be-marketed device in 3.2.P.8. This testing includes device performance testing for spray actuation content, spray content uniformity, spray pattern and droplet size distribution. The stability lots include multiple different storage conditions including accelerated aging conditions. It is noted that in document “stability-summary” that you have provided real time aging to 12 months and accelerated aging for 6 months (at 40 °C). State the equivalent real time age of the accelerated aged lots (6 months at 40°C) and if it is equivalent to the proposed 24 month shelf life.

Sponsor Response:

Hikma acknowledges the Agency’s request to state the equivalent real time age of the accelerated aged lots and if it is equivalent to the proposed 24-month shelf life. Results for all test parameters included in the Naloxone Nasal Spray stability program are in conformance with the acceptance criteria for all primary and supportive stability studies at refrigerated (24 months at 5°C), long term (24 months at 25°C / 60% RH), and accelerated storage conditions (6 months at 40°C / 75% RH), in all orientations. Based on ICH Q1E, 6 months of accelerated and 24 months of real-time stability data have been provided with little to no variability; therefore, a shelf life of 24 months is supported for the product. Additionally, the stability data at room temperature conditions through 24 months for the primary lots manufactured at Insys confirms the performance tests of the device support a 24-month expiry. The updated stability data for the primary lots manufactured at Insys is provided in Module 3.2.P.8.3 of this response supporting that accelerated aged lots (6 months at 40°C) are equivalent to the proposed 24-month shelf life.

FDA Response: The sponsor provided 6 months of accelerated (at 40°C / 75% RH) and 24 months (at 5°C and 25°C/ 60% RH). The testing includes spray actuation content, spray content uniformity, spray pattern and droplet size distribution. All results were within the defined acceptance criteria. Therefore, they have provided stability data to support a shelf life of 24 months for spray actuation content, spray content uniformity, spray pattern and droplet size distribution. **Deficiency resolved.**

Note: they have not provided sufficient accelerated/real-time aging for actuation force, plume geometry, and reliability testing EPRs. These are addressed in another deficiency.

16. You do not define an actuation force specification or include it in your release testing (3.2.P.5.1) of the final finished device. It is noted in document: container-closure-system, that you state that Actuation force performance is approximately (b) (4), but it is unclear if you have identified a specification that is appropriate for the users of your device; i.e. adults and pediatrics, that your device can reliably meet that specification over shelf-life or that you will manufacturer final finished devices that meet this specification. If the actuation force is too high, a user will be unable to actuate the device. Therefore, Provide the following:

- a. Define a specification for actuation force and add it to your release testing (3.2.P.5.1).
- b. Provide the test method that was used to verify device actuation force.
- c. Provide an evaluation of your current testing against the actuation force specification to support the acceptability of your testing.
- d. In Table 7, you list the accelerated aging parameters that were used for specific lots; i.e. 6 months 25°C/60% RH and 6 months 40°C/75% RH. State the equivalent real time age of these accelerated aged lots and if this is equivalent to the proposed 24 month shelf life to support your proposed shelf life.
- e. State how you validated the actuation force specification to demonstrate that the upper specification in part a is appropriate for the intended users of your product.
- f. You have not verified actuation force as a part of your transportation study in test report Report.CH.0142, to demonstrate that the shipping conditions would affect the actuation force of the device. Provide testing verifying the actuation force after shipping.

Sponsor Response:

- a. Hikma acknowledges the Agency's request to define the specification for actuation force. Hikma has updated the proposed drug product release specification limit for actuation force as follows, the mean of the 20 individual units is between (b) (4), with no individual unit > (b) (4). The release data for the three registration batches manufactured at WWCI is provided in Module 3.2.P.5.4 of this response. Additionally, the updated proposed drug product specification is provided in Module 3.2.P.5. and justification of specification is provided in Module 3.2.P.5.6 of this response.
- b. Hikma has provided an analytical procedure to properly verify the device actuation force of the drug product. The revised analytical procedure can be found in Module 3.2.P.5.2 of this response.
- c. Hikma has updated the proposed drug product specification limit for actuation force to the mean of the 20 individual units is between (b) (4) with no individual unit > (b) (4) on release and on stability. The release data for the three registration batches manufactured at WWCI is provided in Module 3.2.P.5.4 of this response. Additionally, the updated proposed drug product specification is provided in Module 3.2.P.5.1 and justification of specification is provided in Module 3.2.P.5.6 of this response.
- d. Hikma acknowledges the Agency's request to state the equivalent real time age of the accelerated aged lots and if it is equivalent to the proposed 24-month shelf life. Results for all test parameters included in the Naloxone Nasal Spray, 8 mg stability program are in conformance with the acceptance criteria for all primary and supportive stability studies at refrigerated, long term and accelerated storage conditions, in all orientations and all strengths. Based ICH Q1E, 6 months of accelerated stability data and 12 months of real-time stability data have been provided with little to no variability; therefore, a shelf life of 24 months is supported for the product. Additionally, the stability data at room temperature conditions through 24 months for the primary lots manufactured at Insys confirms the performance tests of the device support a 24-month expiry. The stability data for the primary lots manufactured at Insys is provided in Module 3.2.P.8.3 of this response.
- e. Hikma proposes the drug product specification limit for actuation force based on acquired data on devices manufactured by Insys and WWCI. The release data for the three registration batches manufactured at WWCI is provided in Module 3.2.P.5.4 of this response. Additionally, the updated proposed drug product specification is provided in Module 3.2.P.5.1 and justification of specification is provided in Module 3.2.P.5.6 of this response. This specification limit is supported by the results of an actuation force study that determined the mean actuation forces achieved by pediatric and adult participants were (b) (4), respectively, with ranges of (b) (4) for children and (b) (4) for adults. This study is reported in journal article Automated actuation of nasal spray products: determination and comparison of adult and pediatric settings (D.V. Doughty et al., Drug Development and Industrial Pharmacy, 2011, 37(2):359-366).
- f. Hikma acknowledges the Agency's request and confirms that a transportation (shipping conditions) study was performed, and Actuation Force was measured on 181 devices. The average force to actuate was measured to be (b) (4) with a range of (b) (4). These results are within the ranges for pediatric and adult patients as listed in the response to Question 16.e. The results support that shipping conditions do not affect the actuation force of the device. Please refer to technical report TRCOL001935, Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report, for the complete data set. The report can be found in Module 3.2.P.2 of this response.

FDA Response:

- a. The sponsor defined the actuation force as the mean of the 20 individual units between (b) (4) with no individual unit > (b) (4). The release specification is as follows: the Mean of 20 units should be within $\pm 10\%$ of the target weight and none of the individual units is outside $\pm 15\%$ of the target weight. It has been added to their release testing. This appears reasonable. **Deficiency resolved**
- b. In 3.2.P.5.2 Analytical Procedures, the sample preparation says it's for the evaluation of spray content uniformity, not actuation force. The sponsor provided the software data processing to measure the important forces but they did not provide the test method for conducting the actuation force test. **IR Deficiency**
- c. In 3.2.P.5.4 Batch Analyses, the sponsor provided the percent range and mean for each lot tested. However, the sponsor did not provide the full results. In addition, the batch analyses note that only (b) (4) units were tested instead of 20. **IR Deficiency**
- d. In 3.2.P.8 Stability, the sponsor only provided 3 months of accelerated and real-time actuation force stability testing in report StbDEV001536. Actuation force was not included in the other two test reports. It is unclear how 3 months of accelerated and real-time aging supports a shelf-life of 24 months. **IR Deficiency**
- e. Validation appears to be insufficient. They validate the specification using a study that references the average actuation force for adults and pediatrics. The range for pediatrics includes forces under (b) (4). They need to validate the specification for a majority of the population, not just the average. **IR Deficiency**
- f. The sponsor provided the verification testing after shipping. The statistical analysis showed that all testing passed. **Deficiency resolved**

17. You do not define a plume geometry specification or include it as part of release testing (3.2.P.5.1) of your final finished device. While you provided plume geometry testing in document: container-closure-system, to demonstrate consistency, it does not appear that you have defined a specification for plume geometry that is needed to ensure that the necessary clinical treatment/effect is delivered appropriately, that your device can reliably meet the specification over shelf life or that you will manufacture final finished devices that meeting this specification. Therefore, provide the following:

- a. Define a specification for plume geometry and include plume geometry to your release testing (3.2.P.5.1).
- b. Provide the test method that was used to verify plume geometry.
- c. Provide an evaluation of your current testing against the plume geometry specification to support the acceptability of your testing.
- d. In Table 2, you list the accelerated aging parameters that were used for specific lots; i.e. 6 months 25°C/60% RH and 6 months 40°C/75% RH. State the equivalent real time age of these accelerated aged lots, and if this is equivalent to the proposed 24 month shelf life to support your proposed shelf life.
- e. You have not verified product plume geometry as a part of your transportation study in test report Report.CH.0142, to demonstrate that the shipping conditions would affect the plume geometry of the drug exiting the device. Provide testing verifying plume geometry after shipping.

Sponsor Response:

- a. Hikma acknowledges the Agency's request to include plume geometry in the proposed drug product release specification. Hikma notes that plume geometry has been well characterized through the testing of registration batches on release and stability, therefore should not be included on the proposed drug product specification.

Hikma notes that this approach is in alignment with FDA guidance Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation which states "the characterization of plume geometry typically should be established during the characterization of the product and is not necessarily tested routinely thereafter." For this reason, Hikma concludes that plume geometry should not be included on the

proposed drug product release specification.

b. Hikma acknowledges the Agency's request to provide the test method used to verify plume geometry. Hikma has provided the test method for plume geometry, refer to "Insys Analytical Procedures, 1927-01-02" in Module 3.2.P.5.2 of this response.

c. Hikma acknowledges the Agency's request to provide the plume geometry evaluation data as well specification limits to support the acceptability of our testing. Hikma notes that plume geometry has been well characterized through the testing of registration batches on release and stability, therefore should not be included on the proposed drug product specification. The plume geometry data for the registration batches for width at (b) (4) ranged from (b) (4). The plume geometry data for the registration batches for angle at (b) (4) ranged from (b) (4). The plume geometry data for the registration batches for width at (b) (4) ranged from (b) (4). The plume geometry data for the registration batches for angle at (b) (4) ranged from (b) (4). Please refer to Module 3.2.P.8.3 of this response for the complete data set.

Plume geometry has been well characterized through the testing of registration batches on release and stability, therefore has not been included on the proposed drug product specification with acceptance criteria. Hikma believes that this is in alignment with FDA guidance Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation which states "the characterization of plume geometry typically should be established during the characterization of the product and is not necessarily tested routinely thereafter." All results generated at Hikma were comparable to the results at Insys for plume geometry. For this reason, Hikma feels that the drug product quality has been successfully characterized and is acceptable.

d. Hikma acknowledges the Agency's request to state the equivalent real time age of the accelerated aged lots and if it is equivalent to the proposed 24-month shelf life. Results for all test parameters included in the Naloxone Nasal Spray stability program are in conformance with the acceptance criteria for all primary and supportive stability studies at refrigerated, long term and accelerated storage conditions, in all orientations and all strengths. Based ICH Q1E, 6 months of accelerated and 12 months of real-time stability data have been provided with little to no variability; therefore, a shelf life of 24 months is supported for the product. Additionally, the stability data at room temperature conditions through 24 months for the primary lots manufactured at Insys confirms the performance tests of the device support a 24-month expiry. The stability data for the primary lots manufactured at Insys is provided in Module 3.2.P.8.3 of this response.

e. A transportation (reliability) study to simulated shipped conditions was performed and plume geometry was measured on 180 devices. The plume geometry data for the registration batches for width at (b) (4) ranged from (b) (4). The plume geometry data for the registration batches for angle at (b) (4) ranged from (b) (4). The plume geometry data for the registration batches for width at (b) (4) ranged from (b) (4). The plume geometry data for the registration batches for angle at (b) (4) ranged from (b) (4). The results support that shipping conditions do not affect the plume geometry of the device. Please refer to technical report TRCOL001935, Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report, for the complete data set. The report can be found in Module 3.2.P.2 of this response.

FDA Response:

- a. The sponsor did not provide the plume geometry as requested. However, this is sufficient as plume geometry is well defined in reliability and release testing according to the Nasal Spray and Inhalation Solution Guidance. **Deficiency resolved**
- b. The sponsor provided the test method to verify plume geometry. **Deficiency resolved**
- c. The sponsor does not define the specification so a comparison of the reliability testing with the specification is not necessary. They do provide the reliability testing for the plume geometry. **Deficiency resolved**
- d. In 3.2.P.8 Stability, the sponsor only provided 3 months of accelerated and real-time actuation force stability testing in report StbDEV001536 and StnDEV001537. It is unclear how 3 months of accelerated and real-time aging supports a shelf-life of 24 months. **Noted in IR Deficiency 16d**
- e. The sponsor provided verification testing after shipping. The statistical analysis showed that all testing passed. **Deficiency resolved**

18. In your product specification sheet for release/shelf life testing in 3.2.P.5.1, you list the droplet size distribution (DSD) and spray pattern of the product at (b) (4) from the outlet of the nasal spray device; however, it is noted in your design verification testing you provided testing of DSD and spray pattern at (b) (4). It appears that (b) (4) is recorded only for informational purposes. Explain why there is no acceptance criteria around DSD and spray pattern at (b) (4) and why DSD and spray pattern does not need to be controlled for during release and stability testing. This discussion should include other controls that are used to ensure that DSD and spray pattern is met at release.

Sponsor's Response:

Hikma acknowledges the agency's request to include droplet size distribution and spray pattern at both (b) (4) distances on the proposed drug product specification and to provide acceptance criteria. Hikma has updated the proposed drug product specification to include droplet size distribution and spray pattern at both (b) (4) distances and has established acceptance criteria. The updated proposed drug product specification is provided in Module 3.2.P.5.1 of this response. Droplet size distribution and spray pattern at both (b) (4) distances were evaluated for the registration batches manufactured at WWCI at release and on stability. Please refer to Module 3.2.P.8.3 of this response for the stability reports of the registration batches manufactured at WWCI.

FDA Response: The sponsor provided release/shelf life testing for (b) (4). They also updated the product specification to include the (b) (4) distance release and stability acceptance criteria. Note, only 3 months of accelerated and real-time stability testing has been performed at this time. It is unclear how 3 months of accelerated and real-time aging supports a shelf-life of 24 months for droplet size distribution and spray pattern. **IR Deficiency**

19. Address the followings regarding your Spray Actuation Content specification:

- a. Your specification for Spray Actuation Content is not aligned with and is wider in terms of the allowable error from the nominal delivery volume, than the recommended specification for pump delivery in The FDA Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (<https://www.fda.gov/media/70857/download>). We recommend that you alter your specification to be aligned with the referenced guidance. Alternatively, justify the clinical relevance of the Spray Actuation Content specification. This justification should rely on the results of your clinical validation testing.
- b. You only propose to test (b) (4) units as a part of the Spray Actuation Content design verification and release testing. It is unclear, how you have determined that a sample size of (b) (4) for design verification and at release, achieves an appropriate level of confidence/reliability for Spray Actuation Content of your product, given the intended use of your product. Provide the following
 - i. Justify the relevance of testing (b) (4) devices as a part of lot release testing.

- ii. With regards, to your spray actuation content verification reliability/confidence, please note that we expect a 99.9% reliability/95% confidence per our previous Type B comments. Please see question 10.

Sponsor Response:

a. Hikma acknowledges that Spray Actuation Content (Pump Delivery) is not aligned with the reference guidance. Hikma has updated the proposed drug product specification to include Spray Actuation Content with established acceptance criteria based on the referenced guidance. The updated proposed drug product specification is provided in Module 3.2.P.5.1 of this response. Spray Actuation Content was evaluated for the registration batches manufactured at WWCI at release and on stability. Please refer to Module 3.2.P.8.3 of this response for the stability reports of the registration batches manufactured at WWCI.

b. i. Hikma acknowledges the request to justify the relevance of testing (b)(4) devices. Hikma has committed to testing 20 units at release and throughout stability to achieve a greater level of confidence/reliability of results for Spray Actuation Content and Spray Content Uniformity. This approach is in alignment with the FDA Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation. Hikma has updated the analytical procedure, Naloxone Nasal Spray, 8 mg/Spray Spray Content Uniformity and Spray Actuation Content by Weight of Naloxone (1927-03), which can be found in Module 3.2.P.5.2 of this response.

b. ii. As noted in the response to question 21, Hikma has performed a new reliability study on a registration/ process validation batch AB0420A. Hikma utilized a statistical methodology for sampling and testing of all EPRs including spray actuation content to demonstrate 99.99% reliability with 95% confidence. Details of the analytical testing results of all EPRs including spray action content and statistical analysis are provided in TRCOL001935, Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report, located in Module 3.2.P.2 of this response.

FDA Response:

- a. The sponsor updated their specification to align with the FDA Guidance. **Deficiency resolved**
b.i. The sponsor increased the sample size to n=20. The Nasal Spray Guidance references n=10 from the beginning and n=10 from the end of containers from a batch. No other reliability/confidence information is provided to support the sample size. **Deficiency resolved**
b.ii. For reliability testing, the sponsor used n=61 test devices to support a 99.99% reliability. The testing resulted in one sample not meeting the reliability specification, likely due to a sample underfilled during packaging (*see Deviation #3 in the reliability test report). The sponsor opened a CAPA to investigate the issue and reduce likelihood of re-occurrence. The sponsor increased the sample size to n=181 to allow for adequate sample powering for k-value calculations and to allow for appropriate representation of population statistic due to rare and justifiable outlier data points. **IR Deficiency**

20. In document "Report.CH.0144", you state that you conducted a fault tree analysis (FTA) with a top-level failure mode of "Device fails to actuate", using your manufacturing/assembly information and failure rate information from your device component supplier dFMEA to support your device reliability. We do not believe that the current FTA supports a 99.99% reliability with 95% confidence for failure to deliver the full intended dose. Address the following comments regarding your FTA:

- a. You state that your top level failure mode for your device within the FTA is "device fails to actuate". As stated in our previous Type B comments that you reference, we recommend that the top level failure mode be "Failure to deliver the full intended dose", as device failing to actuate would be considered a sub-failure mode under failure to deliver the dose.

- b. You do not appear to be considering multiple failure modes that could occur; i.e. failure of one and/or more of the critical components or one of the critical dimensions of the components. This should be included in your FTA.
- c. You are currently referencing the failure modes identified in the device component supplier dFMEA that would affect the device actuator and would result in no dose. This dFMEA includes the manufacturer's approximation for probability associated with the following defects:
- Cannula falls off spray pin
 - Cannula moves during plunger piercing
 - Cannula pierces plunger out of center axis
 - Cannula does not pierce plunger fully.

While the supplied dFMEA provides an approximation of an individual failure rate, the individual failure modes should be incorporated into your FTA, with supporting empirical data referenced to support the failure rate of the top level failure mode. We note that you have supplied incoming component testing and results in test report "Report.CH.0144" where you have characterized the upper and lower specifications for the actuation, holder, stopper and vial, it is unclear how this testing corresponds to the individual failure modes (defined in the dFMEA) affecting the top level failure mode in your FTA. The links between the possible device failure modes that control for the top level failure mode and your process controls to control the components critical to these failure modes are needed to understand how you, as the final to be marketed device manufacturer, are controlling for the top level failure mode to achieve and maintain a 99.99% reliability.

Given that you are proposing to reference a DMF nasal spray device where you may have limited knowledge of device design and/or manufacturing controls, you should define the tolerances of the device components taking into account the individual components and their use in conjunction with associated components of the device that would result in the top level failure mode, then reference your incoming/assembly component testing and results for the device components that could affect the top level failure mode of "failure to deliver the full intended dose" to support the overall reliability in your FTA. Please provide this in an updated FTA, with the summary data that was collected to support the overall reliability.

- d. Based on Table 3 and 4 in document "Report.CH.0144", it does not appear that you are considering for (b) (4) cannula, spray pin, or nozzle in your inspections/in process inspections. Since these appear to be failure modes identified in the component supplier FTA, these should be considered in the FTA for device reliability.
- e. On 9/20/2019, you provided responses to FDA questions stating that "Hikma wishes to inform the Agency that commercial manufacturing will be moved to West-Ward Columbus Inc. (WWCI) in Columbus, Ohio". You have completed your FTA using the device control processes at Insys, not WWCI. Please provide edits to your FTA based on your proposed device control processes at WWCI to demonstrate that your current processes allow for your product to meet a 99.99% reliability for "Failure to deliver the full intended dose".

Sponsor Response:

Hikma acknowledges that the FTA provided by Insys Therapeutics in "Report.CH.0144" did not support a 99.99% reliability with 95% confidence for failure to deliver the full intended dose. We have addressed the following comments regarding our FTA.

- a. Hikma acknowledges your recommendation to change the top-level failure mode within the FTA from "device fails to actuate" to "failure to deliver the full intended dose". Please see Hikma's revised FTA and supporting information in TRCOL001421, 1927- Naloxone Nasal Spray Fault Tree Analysis Report, located in Module 3.2.P.7 of this response. The top-level failure mode was revised from "fails to actuate" to "failure to deliver the full intended dose". Information from

our component supplier and our manufacturing/assembly process were used to support a 99.99% reliability with 95% confidence for failure to deliver the full intended dose.

b. Hikma acknowledges that multiple failure modes that could occur were not captured in the FTA provided in Report.CH.0144 by Insys Therapeutics. Hikma's component manufacturer, (b) (4) provided an FTA with additional details regarding multiple failure modes in TRCOL001421, 1927- Naloxone Nasal Spray Fault Tree Analysis Report, Appendix 1. Additional failure modes were added by Hikma based on our manufacturing/assembly processes and are detailed in the Fault Tree Analysis Report.

c. Hikma acknowledges that the FTA provided in Report.CH.144 by Insys Therapeutics did not provide adequate links between failure modes and controls. As noted in response 20b, additional failure modes were added by Hikma based on our manufacturing/assembly processes and are detailed in TRCOL001421, 1927- Naloxone Nasal Spray Fault Tree Analysis Report. This report also includes the individual failure modes in the FTA, with supporting empirical data referenced to support the failure rate of the top-level failure mode "failure to deliver the full intended dose". Controls at Hikma's suppliers were considered as well as incoming inspection and in-process controls in Hikma's manufacturing, assembly, and final release processes.

Based on Hikma's assessment, the FTA and supporting empirical data support a 99.99% reliability with 95% confidence for failure to deliver the full intended dose. During life cycle management, the product will be monitored for additional faults as well as the probability for the faults that have been defined. Updates to the FTA will be made as needed based on findings from the monitoring or changes at the component manufacturer to maintain 99.99% reliability with 95% confidence for failure to deliver the full intended dose. Monitoring will include manufacturing, packaging, testing and post market surveillance as appropriate. Furthermore, Hikma maintains quality agreements with device suppliers. Per the agreements, suppliers are to notify Hikma of any significant changes to device design and internal FTA. Accordingly, updates to Hikma's FTA will be made as needed.

d. Hikma acknowledges that Tables 3 and 4 in document "Report.CH.0144" by Insys Therapeutics did not consider (b) (4) cannula, spray pin, or nozzle in established inspections/in process inspections. While the measurements do not directly inspect (b) (4) cannula, spray pin, or nozzle these inspections are designed to verify molding consistency. The component mold is maintained by (b) (4) and per the Quality Assurance Agreement between Hikma and (b) (4) will communicate any changes made to the mold or changes to the device to Hikma. Hikma will utilize a change management process to evaluate the change, determine requirements to support the change, and update all relevant documents (i.e. FTA).

e. Hikma moved commercial manufacturing to West-Ward Columbus Inc. (WWCI) in Columbus, Ohio. The FTA provided uses device control processes at WWCI. Based on the proposed device control processes at WWCI, the current processes allow for our product to meet a 99.99% reliability for "Failure to deliver the full intended dose".

FDA Response:

- The sponsor updated the FTA to change the top-level failure mode. **Deficiency resolved**
- The sponsor added additional failure modes and provided additional FTA information for the device components. However, the device component details are provided in a separate FTA from the component manufacturer. The sponsor's FTA should comprise all of the device and component failure modes. **Deficiency resolved**

- c. The sponsor provided the individual failure rates in the FTA. They mention TRCOL001839 Error Probability Inputs in the report but it could not be located in the submission. It is unclear if they provide evidence to support the probability data for each event. They did not define the tolerances of the device components taking into account the individual components and their use in conjunction with associated components of the device that would result in the top level failure mode, then reference the incoming/assembly component testing and results for the device components that could affect the top level failure mode of “failure to deliver the full intended dose” to support the overall reliability in the FTA. They only rely on the QA agreements with the suppliers. **IR Deficiency**
- d. The sponsor confirmed that they are not considering for (b)(4) cannula, spray pin, or nozzle in your inspections/in process inspections and therefore, are not considered in the FTA. They rely on the QA of the component manufacturer to verify molding is maintained. They state that they will implement a change management process to evaluate the change but do not provide further information regarding the change or any additional information to support the FTA. **IR Deficiency**
- e. The sponsor stated that the FTA provided uses device control processes at the WWCI manufacturing facility. They provide their reliability testing to support the 99.99% reliability. **Deficiency resolved**

21. To support verification of your system level reliability you provide Spray Actuation Content performance testing in document: “Report.CH.0144”. You state “Insys tested at least 480 devices each from two lots of combination product packaged in 20 shippers each to verify reliability”. Address the following comments regarding your protocol:

- a. Explain the statistical methodology behind the inclusion of 480 devices from two lots and how this equates to a 99.99% reliability with 95% confidence for spray actuation content.
- b. You do not provide testing of the device essential performance requirements (EPRs) to a 99.99% reliability with 95% confidence, as recommended in the previous Type B comments. As stated in our previous Type B comments, the Agency considers Spray Actuation Content/Dose Accuracy, Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force to be the EPRs for your device type, as these performance requirements are necessary for your device constituent to safely and effectively achieve the combination product’s intended use; therefore we recommend that you provide verification testing to support a 99.99% reliability with 95% confidence for these specific EPRs.
- c. It is noted that you state that one lot was the (b)(4)% alcohol product and the other was the to-be-marketed 20% alcohol product. It is unclear how the use of the (b)(4)% drug product is applicable to support the reliability of the 20% product. While the device may be the same, the use of the different drug product could potentially influence the drug spray characteristics. Provide justification why using the (b)(4)% drug product would not impact the drug spray characteristics.
- d. You state that all devices were exposed to accelerated aging conditions (40°C 75%RH for at least 6 months). State the equivalent real time age of these accelerated aged lots, and if this is equivalent to the proposed 24 month shelf life to support your proposed shelf life. Note that we expect that the devices tested in the reliability study will support the shelf life of the product.

Sponsor Response:

- a. Hikma acknowledges the Agency’s observation for the lack of justification from Insys Therapeutics Inc (Insys) for selecting a sample size of n = 480 devices to demonstrate 99.99% reliability with 95% confidence. Hence, Hikma decided to repeat the reliability study with a new approach utilizing a statistical methodology. Sample size and method to demonstrate 99.99% reliability with 95% confidence is based on a probabilistic approach detailed in TRCOL001935 located in Module 3.2.P.2 of this response.

The probabilistic method selected by Hikma is to determine a tolerance-based k value for each essential performance requirement (EPR): Spray Actuation Content/Dose Accuracy, Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force. The target k value is defined as the “tolerance factor” appropriate to the number of samples tested, to the confidence (level), and to the reliability (limits) of interest. The target k value therefore varies based on the sample size, confidence interval, and desired reliability value. The target k value for different sample sizes and reliability results is calculated via standard equations and can be found in look-up tables documented in various literature and standardized testing methods (e.g. ISO 11608-1). Furthermore, for each EPR an empirically derived k value (known as the kactual) is calculated based on the actual testing results. The equations for calculating kactual value are provided in various literature and documented in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. To calculate the final reliability results, the empirically derived kactual value is compared to k-value; if kactual value meets or exceeds the target k value then the targeted reliability & confidence level is demonstrated (99.99% reliability with 95% confidence).

Additionally, to determine whether a selected sample size is appropriate for calculating the kactual value and demonstrating reliability, an average power assessment was performed for all EPRs. An average power study was performed using a Shapiro-Wilks test on previous data generated from lots manufactured by Insys and WWCI transfer lots to determine an appropriate sample size for the functional reliability testing. The results provided the minimum sample size (n) needed for a 99% powering (P) i.e. probability that the test results in success. It was determined via the Shapiro-Wilks test method that all EPR tests can use a sample size of n=60 for kactual value calculation to demonstrate the desired reliability. Sample size n=60 is based on the worst case of n=27 for P = 0.99 for the EPR of droplet size (b) (4) D90; nearly double the worst-case sample size is conservatively selected for each test and scenarios defined in TRCOL001935 (total number of samples tested for reliability studies is 1081) to account for any variability from testing methods and to provide adequate sample powering to calculate the k value statistic. Additionally, for applicable EPRs, increased number of data points were analyzed by combining data points from all scenarios in order to increase sample size powering due to rare and justifiable outliers and higher inherent variability in data. Analysis details are described in TRCOL001935. Following the aforementioned approach, the kactual value for all EPRs (WWCI registration lot AB0420A,) was calculated and found to be greater than or equal to their respective target k-value. Results and rationale of all reliability testing are summarized in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. Hence all targeted EPRs demonstrate 99.99% reliability at a 95% confidence level.

b. Hikma acknowledges the agency’s feedback that Insys did not test all essential performance requirements (EPRs) to a 99.99% reliability with 95% confidence. In the new reliability study performed by Hikma, all EPRs identified in the Type B meeting (Spray Actuation Content/Dose Accuracy, Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force) were targeted for testing per the specifications and statistical acceptance criteria detailed in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. For all EPRs, kactual value was calculated and compared to a target k-value to demonstrate 99.99% reliability with 95% confidence. Reliability testing results for all EPRs and calculated kactual values are summarized in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. The report is located in Module 3.2.P.2 of this response.

c. Hikma acknowledges that the (b) (4) % alcohol formulation could potentially influence the drug spray characteristics. Hence, in the new reliability study initiated by Hikma, only the 20% alcohol

formulation, which is intended for commercial distribution, is included for testing per TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. Unlike Insys, Hikma did not pursue the justification to utilize the testing data from the (b) (4) % alcohol formulation to support the reliability study conclusion.

d. In the new reliability study performed by Hikma, the Combination Product (device) was aged in preparation for reliability testing on Essential Performance Requirements (EPRs). Accelerated aging of the devices was performed in the final representative configuration to simulate the effects of aging on the device at the end of shelf life.

Aging model for drug products to predict Controlled Room Temperature (CRT) shelf life described in ICH Q1 is selected by Hikma to determine the accelerated aging conditions. This model is used to predict shelf life at CRT to be 24 months if stored at accelerated conditions for a specific amount of time. This model assumes the kinetic factor is 2 times rate of degradation per 10°C increase in temperature. In this model, the lower range of CRT (20°C) is used as the baseline storage temperature.

The accelerated aging time is calculated using the following equation: (See pdf)

Using the above equation, the calculated accelerated aging time is 91 days. Therefore, accelerated aging at 50°C/75%RH for 3 months was deemed as appropriate to demonstrate equivalency to samples aged for 24-months.

Reliability samples aged for 3 months at 50°C/75%RH were tested as part of the reliability testing plan. Testing results met the statistical acceptance criteria to demonstrate 99.99% reliability at 95% confidence of all EPRs and are summarized in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. Hence, the reliability study performed by Hikma with aged samples supports the shelf life of 24 months for the combination product.

FDA Response:

- a. The sponsor's approach to re-perform reliability testing using k-values and a sample size of n=60 to support 99.99% reliability, 95% confidence is acceptable. **Deficiency resolved**
- b. The sponsor performed Spray Actuation Content/Dose Accuracy, Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry and Actuation Force reliability testing to support 99.99% reliability, 95% confidence. **Deficiency resolved**
- c. The sponsor removed the (b) (4) % alcohol formation and only performed reliability testing using the 20% alcohol formulation, which is intended for commercial distribution. This addresses our concerns. **Deficiency resolved**
- d. The sponsor's justification for accelerated aging at 50°C/75%RH for 3 months appears uses 20°C when the real-time aging is evaluated at 25°C. Therefore, their justification is inadequate and they should perform longer accelerated testing to support a shelf life of 24 months. **IR Deficiency**

22. To support verification of your system level reliability you provide spray actuation content performance testing in document: "Report.CH.0144". Address the following questions about your test results:

- a. You state that 10 devices out of 540 devices exhibited separation between the vial and vial holder. While you state that the devices delivered the proper dose, a user may not understand how to reconnect the vial and vial holder with the device, prior to use in an emergency/high stress use environment. You state that the root cause of the failure was the "shipping drop test not being performed as per the protocol." Provide more details regarding the root cause determination and why this drop testing that resulted in vial/vial holder separation would not occur during a typical use/shipping scenario.

- b. In the Lot 1036107 visual inspection after preconditioning, you state that one device was found to have a loose vial holder (plunger), where the bridges connecting the plunger to the actuator were broken, which was caused by higher impact stress applied during simulated shipping. Given the description that the product contained a loose plunger, it sounds reasonable that if the plunger was to be loose, that it could detach from the device constituent, and could result in device failure. Explain how you came to the conclusion that, “it was suspected that the loose vial plunger would not affect functionality.”
- c. Referring to the issues noted above, you state: “In order to mitigate this kind of damage to the device, shipping procedures will be reviewed further, and additional controls will be added prior to commercial launch if appropriate”. In both cases above, it appears that the preconditioning used in the reliability verification testing resulted in the potential failure modes noted above. Given these potential failure modes noted, provide additional controls to mitigate the risk of vial and vial holder separation and testing demonstrating that they are effective.

Sponsor Response:

a. Hikma purchased the NDA 505(b)(2) from Insys Therapeutics Inc (Insys) as part of bankruptcy proceedings. Hikma did not contribute towards the initial reliability study plan adopted by Insys. Hikma performed an assessment of the reliability study design upon transfer from Insys and concluded that it was inadequate. Hence, as noted in responses to question 21, Hikma performed a new reliability study following a statistical methodology and standardized testing method to demonstrate reliability. Hikma’s reliability study design incorporated a simulation of worst-case reasonably foreseeable conditions seen under shipping and storage, while in possession of the patient or care giver, as well as conditions seen just prior to device activation. Hence, all reasonably foreseeable scenarios that can occur during a) shipping and storage, b) handling and storage and c) just prior to use were incorporated for pre-conditioning. Pre-conditioning details for all three scenarios are provided in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report, located in Module 3.2.P.2 of this response.

Hikma packaged the devices from one of the registration/process validation lots (AB0420A) in final representative configuration of the finished product for bulk shipping (shipper boxes) and patient use (cartons). These devices were subjected to accelerated aging at 50°C/75%RH for 3 months. Subsequently, blistered devices in Shipper Boxes and Cartons were subjected to temperature excursion cycling, vibrations, and pressure simulation using ASTM test methods; furthermore, samples from scenario 2 and scenario 3 were subjected to drop testing. Preconditioning details for all three scenarios are provided in TRCOL001935.

The pre-conditioned devices were subjected to visual inspection post-stressing at the testing site, (b) (4) and upon receipt at Hikma in Columbus, OH. Visual inspection results are detailed in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. Visual inspection resulted in zero damaged devices similar to the defect documented by Insys in CH.0144 (no devices had separation of the vial and vial holder from the actuator). Furthermore, these devices were analytically tested for all EPRs per the reliability specifications provided in TRCOL001935. Testing results met the statistical acceptance criteria to demonstrate 99.99% reliability at 95% confidence of all EPRs and are summarized in TRCOL001935.

Insys reliability study (CH.0144) reported a deviation during the shipping simulations study that resulted in excessive stressing of the samples: For Sequence # 2 and # 8 Manual Handling-Drop test was conducted at Assurance Level I instead of Assurance level II. For Sequence # 2, this resulted in use of drop height of (b) (4) instead of (b) (4) and for Sequence # 8 use of drop height of (b) (4) instead of (b) (4). This deviation resulted in the 10 damaged devices. These deviations were not

noted during the shipping simulation performed at (b) (4) on reliability samples from Hikma.

Additionally, Insys' study incorporated only a single scenario of shipping of devices in shipper boxes and stress- testing them for vibration and shock handling conditions per ASTM D-4169-16; the stressed devices were analytically tested only for Spray Actuation Content. However, Hikma's reliability study incorporated multiple scenarios of pre-condition and consecutive stressing of devices. Further, Hikma's reliability testing incorporated testing for all EPRs: Spray Actuation Content/Dose Accuracy, Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force. Hence, it can be concluded that Hikma's stress conditions and testing plan were more robust and stringent compared to that of Insys' reliability study. Despite the excessive stress testing, no damage to the devices was observed during visual inspection and analytical testing of EPRs at Hikma.

Therefore, Hikma concludes that the shipping of devices during commercial shipments and transportation during or prior to patient/care-giver's use is found to be acceptable in the current packaging/ shipping configuration and typical use/shipping scenarios.

b. Insys' reliability study report was reviewed by Hikma and the study design was found to be inadequate. Hence, as noted in question 22a, Hikma performed a new reliability study. Per the new reliability study design, the devices were subjected to a series of stress conditions expected during different scenarios during shipping, storage and use of devices as detailed in TRCOL001935.

Reliability device samples in shipper boxes stressed at (b) (4) were visually inspected upon receipt at Hikma before they were subjected to analytical testing. Devices did not show damage to the vial holder, bridges connecting the vial holder to actuator, or to other aspects of the device. Damage to the vial holder, bridges connecting the vial holder to actuator, or to other aspects of the device was also not reported during the analytical testing of reliability sample devices from these shippers. Furthermore, devices in cartons were also stressed per TRCOL001935 and visually inspected for damage upon receipt at Hikma. Additionally, samples from scenario 2 and 3 are subjected to drop testing as detailed in TRCOL001935 and visually inspected for damages. Damage to vial holder, bridges connecting the vial holder to actuator, or to other aspects of the device was also not reported during the analytical testing of reliability sample devices from these cartons. Based on these findings, Hikma concluded that the current packaging configuration and labeled instructions for use of devices are acceptable to prevent damage during shipping or handling.

c. As noted in responses to question 22a & 22b, Hikma repeated the reliability testing and the visual inspection results did not show damage to the vial holder, bridges connecting the vial holder to actuator, or other aspects of the device. Further, analytical testing of reliability samples demonstrates that the EPRs meet the targeted 99.99% reliability at 95% confidence. Reliability testing results are detailed in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. Hence, Hikma concluded that the current packaging configuration and typical use/shipping scenarios of devices are acceptable and additional controls to mitigate the risk of vial and vial holder separation are not required.

FDA Response:

- a. The sponsor identified all of the issues noted in the previous manufacturer's reliability testing. This information is adequate to support that the vial/vial holder separation would likely not occur during a typical use/shipping scenario. **Deficiency resolved**
- b. The sponsor re-iterated the issues found with the previous manufacturer's reliability testing. The sponsor provided an adequate explanation to support their new reliability. **Deficiency resolved**

c. The sponsor did not provide additional controls to mitigate the risk of vial and vial holder separation that was an issue in the prior manufacturer's reliability testing. Instead, they stated that they repeated reliability testing and visual inspection did not show damage to the device. The changes in drop testing appear reasonable. Since they re-performed the reliability testing and no issues arose, no additional mitigations are necessary. **Deficiency resolved**

23. On 9/20/2019, you provided responses to FDA questions stating that "Hikma wishes to inform the Agency that commercial manufacturing will be moved to West-Ward Columbus Inc. (WWCI) in Columbus, Ohio". You have completed your device performance/reliability verification testing on product that was manufactured/assembled at Insys, not WWCI. Provide process validation testing to demonstrate that the new processes at WWCI will allow the device to meet its essential performance requirement (EPR) specifications at a 99.99% reliability and 95% confidence: Spray Actuation Content, Dose Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force. The process validation testing may include additional device verification testing at the WWCI manufacturing site to demonstrate that the device EPRs meet their respective specifications and reliability specifications.

Sponsor Response:

As noted in response to Question 21 and 22, Hikma has performed a new reliability study on a registration/process validation batch AB0420A manufactured at WWCI. A statistical methodology was implemented to design the reliability study. Reliability testing was performed on all the EPRs (Spray Actuation Content, Dose Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force). Testing results were analyzed using a probabilistic approach (tolerancebased k value) to demonstrate 99.99% reliability and 95% confidence. Reliability testing results are summarized in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. The report can be found in Module 3.2.P.2 of this response.

Furthermore, to demonstrate successful process transfer from Insys to Hikma, process validation was performed on three commercial scale lots with additional testing of EPRs per TRCOL001055 1927 – Registration / Transfer / Process Performance Qualification Report for Naloxone Nasal Spray, 8 mg. This report can be found in Module 3.2.P.2 of this response. Testing results of EPRs from process validation lots show that they meet the pre-determined acceptance criteria in the finished product specification and are summarized in TRCOL001055. Process Validation lots were placed on room and 5°C temperature and accelerated stability; testing results for all time points available at the time of submission meet the stability specifications and are summarized in the following stability reports: STABCOL000152, StbDEV001536, and StbDEV001537, which are located in Module 3.2.P.8.3 of this response.

FDA Response: The sponsor re-performed reliability testing at the new facility. They also performed process validation on three commercial scale lots with 200 units each (the correct file is TRCOL001827). They report the sample size for throughout the run Spray Actuation Content as n=20. **IR Deficiency**

- 2) Specific to your October 18, 2019 IR response to FDA question #21c, you provide a justification to support using one lot of the (b)(4)% alcohol formulation as a part of your reliability study. While we acknowledge that the to-be-marketed 20% alcohol formulation was used as well, you did not provide an adequate justification to support using the (b)(4)% alcohol formation to support the reliability of the to-be-marketed 20% alcohol formulation. In your justification you state: "*Hikma acknowledges that the (b)(4)% alcohol formulation may have slightly different spray characteristics compared to that of the 20% alcohol formulation due to minor differences in (b)(4) solution properties including viscosity, specific gravity, and density*". Given that the spray characteristics will likely be influenced by the alcohol content in the respective drug product, we recommend that Spray Actuation Content/Dose Accuracy, Spray Pattern, Spray Content Uniformity, Droplet Size

Distribution, Plume Geometry, and Actuation Force reliability verification testing be completed with the to-be-marketed 20% alcohol formulation of your product.

Sponsor Response: Hikma acknowledges the Agency's request and has performed a new reliability study on registration/ process validation batch AB0420A (20% alcohol formulation) using a statistical methodology to demonstrate 99.99% reliability with 95% confidence. Hikma did not pursue the initial approach followed by Insys to incorporate one lot with (b) (4) % alcohol formulation as part of the reliability study since the (b) (4) % alcohol formulation is not intended for marketing. Instead, the reliability study sampling and testing plan was designed to incorporate only the to-be-marketed 20% alcohol formulation.

Per the study, reliability testing was performed on all EPRs (Spray Actuation Content, Dose Spray Pattern, Spray Content Uniformity, Droplet Size Distribution, Plume Geometry, and Actuation Force). Testing results were analyzed using a probabilistic approach (tolerance-based k value). Reliability testing results are summarized in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report and demonstrate 99.99% reliability and 95% confidence for all EPRs. This report can be found in Module 3.2.P.2 of this response

FDA Response: The sponsor performed the reliability testing using only the 20% alcohol formulation.
Deficiency resolved

- 3) Specific to your October 18, 2019 IR response to question #24d, you provide a brief summary of your CAPA procedure and reference to your internal CAPA procedure; however, there is limited detail regarding your CAPA procedures and a determination of the adequacy of the procedure cannot be made. Provide your internal CAPA procedure for our review. Ensure that your procedure includes the following elements:
- 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.
 - 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.
 - Appropriate statistical analysis of these quality data to detect recurring quality problems
 - Investigations into the cause of nonconformities relating to product, processes, and the quality system
 - Requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems
 - 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
 - Procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications
 - Requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems
 - 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
 - Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review
 - Requires documentation of all CAPA activities

Sponsor Response: Hikma acknowledges that our response on Oct 18, 2019 did not provide adequate details to demonstrate compliance with 21 CFR 820.100. To address this, we are providing procedure

SOPCOL000069, Corrective and Preventive Action. This procedure can be found in Module 3.2.P.2 of this response. Please note that sections I through XI of SOPCOL000069 address questions a through k, respectively. Our procedure is aligned with 21 CFR 820.100 Corrective and Preventive Action.

FDA Response: The sponsor identified how they met all elements, a through k, in their CAPA SOP.
Deficiency resolved

12.2. Resubmission Information Requests (IR)

Information Request #1 was issued on 2/12/2021. Sponsor provided a response on 3/5/2021.

1. In response to Deficiency #16, we have the following concerns regarding your actuation force specification:

- a. Deficiency #16b: In 3.2.P.5.2, the actuation force report references the evaluation of spray content uniformity under sample preparation and not actuation force. In addition, you provided the software data and data reporting, but you did not provide the test method for conducting the actuation force test. You should update the sample preparation to reflect the actuation force test and provide the full test method that was used to verify the device actuation force.

Sponsor Response: Hikma acknowledges the Agency's request and would like to clarify that the analytical procedure for Actuation Force, 1927-02-02, provided in Section 3.2.P.5.2 of the application, states to process the same 20 actuations (1 per device) that were utilized for the evaluation of Spray Content Uniformity (SCU). The same sample preparation as per analytical procedure for Spray Content Uniformity and Spray Actuation Content by Weight of Naloxone, 1927-03-01, also provided in Section 3.2.P.5.2 of the application, is used to evaluate actuation force. The analytical procedure for Actuation Force describes how to process the actuation force data that is collected using the (b) (4) Software during the SCU sample preparation using the (b) (4) Actuator. Therefore, the analytical procedure for Actuation Force does not need to be updated, as the sample preparation is provided in the SCU analytical procedure and referenced in the Actuation Force analytical procedure.

FDA Response: The sponsor noted that the test procedure for the actuation force is the same as the Spray Content Uniformity and Spray Actuation Content tests. This is sufficient. **Deficiency resolved**

- b. Deficiency #16c: In 3.2.P.5.4, you provided the release data results for three registration batches. However, your testing was only performed on (b) (4) individual units and not 20 units as specified in your updated actuation force specification. You also did not provide the full test results. You should perform the actuation force testing using the number of units identified in your specification and compare the results against the actuation force specification to support the acceptability of your testing.

Sponsor Response: Hikma acknowledges the Agency's request and would like to clarify that a total of 40 individual units were tested for actuation force at release; 10 individual units were tested from the beginning of the manufacturing process (BOR, beginning of run), 10 individual units were tested from the middle of the manufacturing process (MOR, middle of run), 10 individual units were tested from the end of the manufacturing process (EOR, end of run) and 10 individual units were tested from the composite sample (contains random samples from BOR, MOR and EOR). The certificates of analysis for all three registration lots at release presented a total of 20 individual units for actuation force, containing 10 individual results from BOR and 10 individual results from EOR. Hikma will continue to perform actuation force testing on 20 individual units as per the specification for all future lots at release and throughout stability.

FDA Response: The sponsor confirmed that 40 units were tested, not just (b) (4). 20 will be tested on all future lots at release through stability. The sponsor still did not provide full test results; however, they attest to their certificate of analysis which has a summary of the results. This is sufficient. **Deficiency resolved**

- c. Deficiency #16d: In 3.2.P.8.3, you only provided 3 months of accelerated and real-time actuation force stability testing. Your justification stating that there is little to no variability in the stability data is insufficient to support a shelf life of 24 months. You should perform additional accelerated testing and provide justification to support a shelf life of 24 months.

Sponsor Response: Hikma acknowledges the Agency's request to perform additional accelerated testing to support the proposed 24-month shelf life and would like to confirm that accelerated stability testing through 6 months and room temperature testing through 9 months has been completed. The updated stability report for the registration lots manufactured at West-Ward Columbus Inc. (WWCI) is provided in Section 3.2.P.8.3 of this response.

FDA Response: The sponsor performed 6 months of accelerated actuation force stability testing. This is sufficient to support a shelf life of 24 months. **Deficiency resolved**

- d. Deficiency #16e: Your validation to support the actuation force specification limit is insufficient. You reference an actuation force study that determined the mean actuation forces in adults and pediatrics. Your actuation force specification should ensure that the majority of the population can use the device, not just the average user. Using the mean actuation force to validate your specification indicates that the specification may be too high for some users. You should provide validation for the actuation force specification limit to support that the specification is appropriate for the majority of the intended users of your product.

Sponsor Response: Hikma acknowledges the Agency's request and would like to clarify that the Agency's previous request to define the specification for actuation force has been accepted and adopted. Hikma proposed the following acceptance criteria for actuation force: the mean of the 20 individual units is between (b) (4), with no individual unit > (b) (4). Hikma has set these criteria to ensure that the majority users of the Naloxone Nasal Spray product have the ability to actuate the device. A limit of not more than (b) (4) for actuation force is well within the user's ability to actuate the device independent of age or gender. By utilizing the mean of the 20 individual units, Hikma is further controlling the actuation force to limit the variability of the device.

Hikma's Human Factor Validation Study located in Section 1.14.1.4 of the application, concluded that the Naloxone Nasal Spray Device has been found to be easy to use for the intended users in an emergency environment. The device was tested with a panel of thirty (30) subjects – fifteen (15) adolescents (ages 10 to 17) and fifteen (15) adults (ages 21 to 66). During the study, all test subjects pressed the plunger to release a full dose for the first dose and second dose (if a second dose was given). The subjects did not have difficulty actuating the device independent of age or gender. Likewise, one subject stated, "Package was easy to open and didn't have to put a lot of pressure on the plunger", further demonstrating the minimal force required by the actual user to actuate the device.

Various journal articles were reviewed by Hikma when establishing the actuation force limits. The following articles and summaries were taken into consideration:

- The actuation force study provided in the journal article (D.V.Doughty et al., Drug Development

and Industrial Pharmacy, 2011, 37(2):359–366), determined the mean actuation forces achieved by pediatric and adult participants were (b) (4) respectively, with ranges of (b) (4) for children and (b) (4) for adults.

- The actuation force study provided in the journal article (Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. Am J Occup Ther. 1986 Oct;40(10):705-11. doi: 10.5014/ajot.40.10.705. PMID: 3777107), determined the average performance of normal subjects on the Palmar Pinch grip, the same grip utilized to dose the Naloxone Nasal Spray Device. The lowest mean grip strength observed in the intended user adolescents age group (10 to 11 years old) was in the female population utilizing their left hand, requiring a mean actuation force of (b) (4) with a standard deviation (SD) of 2.0. Evaluating the mean minus 1SD as the worst case, the mean actuation force results to (b) (4)

- The actuation force study provided in the journal article (Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985 Feb;66(2):69-74. PMID: 3970660), determined the average performance of normal adult subjects (310 male and 328 female adults, ages 20 to 94) on the Palmar Pinch grip, the same grip utilized to dose the Naloxone Nasal Spray Device. The lowest mean grip strength observed in the intended user adult age group (up to 70 years old) was in the female population, requiring a mean actuation force of (b) (4) with a SD of 3.7 across all females of all ages (20 to 94). Evaluating the mean minus 1SD as the worst case, the mean actuation force results to (b) (4)

By employing the mean minus 1 standard deviation approach as worst case for the 10 year old and 70 year old populations, based upon literature data, Hikma concludes that the majority of users are confidently able to actuate the device with the specification of NMT (b) (4) for any individual device. Further, Hikma notes that the mean actuation force specification limit of (b) (4) further confirms that the majority of devices produced by Hikma require lower than (b) (4) force to actuate.

The release and stability data collected on both the Insys and WWCI manufactured registration lots support the actuation force limits, as no individual device has required an actuation force of more than (b) (4) and the mean data for all registration lots at release and throughout stability have been between (b) (4). The users of the Naloxone Nasal Spray product can actuate the device, as the actuation force of not more than (b) (4) is well within the majority of user's ability to actuate the device independent of age or gender.

FDA Response: The sponsor only provided validation using 1 Standard Deviation (SD) which covers 68% of the population. They should include 2 SDs to cover 95% of the population. They also did not provide the studies in full. See **IR #2**

2. In your response to Deficiency #17d via 3.2.P.8.3, you only provided 3 months of accelerated and real-time plume geometry stability testing. Your justification stating that there is little to no variability in the stability data is insufficient to support a shelf life of 24 months. You should perform additional accelerated testing and provide justification to support a shelf life of 24 months.

Sponsor Response: Hikma acknowledges the Agency's request to perform additional accelerated testing to support the proposed 24-month shelf life would like to confirm that accelerated stability testing through 6 months and room temperature testing through 9 months has been completed. The updated stability report for the registration lots manufactured at WWCI is provided in Section 3.2.P.8.3 of this response.

FDA Response: The sponsor provided 6 months of accelerated plume geometry stability testing. This is sufficient to support a shelf life of 24 months. **Deficiency resolved**

3. In response to Deficiency #19b.ii via 3.2.P.2, you provided the reliability study to include the sampling of the spray actuation content. However, you note in Deviation #3 that the sample size was increased following a sample error. You opened a CAPA to investigate the issue but the CAPA was not provided to verify that adequate mitigations were implemented to prevent further device errors. You should provide the CAPA for the spray actuation content testing.

Sponsor Response: Response

Hikma acknowledges the Agency's request to provide CAPAs referenced in deviation #3 in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report. CAPAs were opened as a result of the investigation of one (1) sample with low spray actuation content (SAC) and spray content uniformity (SCU) results, which contributed to the need to increase sampling to demonstrate reliability performance. (b) (4)

(b) (4) Hikma still opened multiple CAPAs to evaluate mitigation strategies (b) (4) to ensure sustainable reliability performance. (b) (4)

(b) (4)

The above CAPAs will be implemented on future commercial lots to show CAPA effectiveness and

ensure that reliability performance is consistently maintained.

(b) (4)

FDA Response: The CAPAs appear sufficient to mitigate the risk of low spray actuation content and spray content uniformity. The mitigations appear adequate. **Deficiency resolved**

4. In response to Deficiency #20, we have the following concerns regarding your fault tree analysis (FTA):
- a. Deficiency #20c: You mention the TRCOL001839 Error Probability Inputs in the FTA report but the document could not be located in your submission. You have not provided evidence to support the probability data for each event. Additionally, you have not defined the tolerances of the individual device components and the incoming/assembly component testing and results. You rely on the QA agreements from the supplier, but this is insufficient to support your FTA. Please provide TRCOL001839 as well as evidence to support the probability data for each event. You should use tolerances of the individual device components identified by the supplier and add incoming/assembly component testing to support the overall reliability of your FTA.

Sponsor Response: Hikma acknowledges the Agency's request to provide the report - TRCOL001839: 1927 – Error Probability Estimate Inputs into FTA Naloxone Nasal Spray, 8 mg/spray and device component testing strategy to support overall reliability of FTA. Report TRCOL001839 is provided in Section 3.2.P.7 of this response. Report TRCOL001839 provides the justification for error probability values of multiple error descriptions/ events related to device and drug formulation performance that are provided in the FTA reported in TRCOL001421: 1927 - Naloxone Nasal Spray, 8 mg per Spray Fault Tree Analysis Report which is located in Section 3.2.P.7 of the application. The remaining error probability values that are solely attributed to the device performance are directly obtained from the device vendor (b) (4) since device sub-components (e.g. cannula, spray pins etc.) are assembled at (b) (4) and they maintain the process quality control information. (b) (4) error probability estimates are provided in Section 11 of TRCOL001421. Overall, reports TRCOL001839 and TRCOL001421 contain the justification for the error probabilities of all individual error events described in the FTA.

In addition to QA agreements with component vendors, Hikma has established adequate incoming quality control testing of individual device components prior to release in packaging. Registration/ process validation lots were successfully tested per this quality control process and reliability performance of all device EPRs at 99.99% at 95% confidence levels was demonstrated per TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report which is located in Section 3.2.P.2 of the application. Further, Hikma coordinated with the device vendor (b) (4) to align with their in-house quality control program and testing prior to shipment to customers to ensure that device quality is repeatable and reliability performance is sustainable during routine production. (b) (4) maintains the critical device design drawings/ specifications, dimensional tolerances, and process control data as proprietary information that are not available to customers. However, (b) (4) has confirmed that they have established statistical in-process controls (b) (4) and 100% in-line auto-inspection of critical device dimensions and critical functional attributes of the device during routine production. (b) (4) current in-process controls and long history of device production experience justifies the low probability of various error events described in their FTA reports. To ensure conformity, Hikma can

review (b) (4) process quality control data and other supporting information relating to reliability performance during annual site audits per the current QA agreement. Hence, Hikma deems that the current process quality controls and testing at (b) (4) and incoming testing of device components adequately supports the reliability performance as calculated in the FTA.

FDA Response: The sponsor provided the report TRCOL001839 Error Probability Inputs. This, along with (b) (4) TRCOL001421 probability data, is sufficient to address the probability data for each event in the FTA.

While they did not provide the tolerances of the individual device components, the sponsor is performing incoming quality control on individual device components prior to release and the device vendor (b) (4) is performing in-process controls as well as 100% in-line auto-inspection of critical device dimensions and functional attributed. This appears sufficient. **Deficiency resolved**

- b. Deficiency #20d: You are not considering for (b) (4) cannula, spray pin, or nozzle in your established inspections/in process inspections and therefore, these components are not considered in the FTA. You state that you will implement a change management process to evaluate the change but do not provide further information regarding the change or any additional information how this change will support the FTA. You should provide your change management process and what requirements will be implemented to support the change.

Sponsor Response: Hikma acknowledges the Agency's comments on established in-process inspections, error events in FTA and internal change management process for device components. We note that the FTA described in TRCOL001421: 1927 - Naloxone Nasal Spray, 8 mg per Spray Fault Tree Analysis Report, located in Section 3.2.P.7 of the application, already incorporates error events related to (b) (4) cannula, spray pin, or nozzle. For example, refer to (b) (4) TRCOL001421.

As noted in response to question 4a, the device supplier (b) (4) has established in-process controls during production of devices. (b) (4)

(b) (4)

(b) (4)

FDA Response: The sponsor confirmed that they incorporated error events related to (b) (4) cannula, spray pin, or nozzle in the FTA. The device supplier also included in-process controls and inspects for the cannula and spray pin for every product on release. The sponsor updated their inspection process to (b) (4) detect defects related to the canula or other critical parts. This appears sufficient to support the reduction of error events related to (b) (4) cannula, spray pin and nozzle. **Deficiency resolved**

5. In response to Deficiency #21d, you provided calculations to justify that your accelerated aging supports a shelf life of 24 months for your reliability study of the EPRs. However, your calculations include the controlled room temperature as 20°C when your real time aging is performed at 25°C. Since the accelerated aging should represent worst-case, you should use 25°C in your calculations. With an accelerated temperature of 50°C and a controlled room temperature of 25°C, the calculated accelerated aging time would be 129 days to support a shelf life of 24 months. You should perform additional accelerated aging testing to support a shelf life of 24 months.

Sponsor Response: Hikma acknowledges the Agency's advice of utilizing 25°C for controlled room temperature (CRT) as worst-case condition in the accelerated aging model calculations. We acknowledge that the use of highest range of CRT (25°C) equates to a requirement of 129 days of storage time in chambers at 50°C to support a shelf life of 24 months. Hikma used CRT of 20°C in our accelerated aging model calculations since it was within the allowable range for CRT conditions. Hence samples were aged for 91 days at 50°C. However, Hikma acknowledges that utilizing the higher end of the CRT range (25°C) could demonstrate a theoretical worst-case condition for simulated aging in the stability chambers by allowing extended period of exposure of samples (aging) to high temperature.

As demonstrated in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report, located in Section 3.2.P.2 of the application, reliability samples aged for 91 days and subjected to different stress conditions successfully demonstrated reliability performance of 99.99% at 95% confidence level for all EPRs.

We note that the difference in storage time requirement in stability chambers between the use of CRT of 25°C and 20°C in the accelerated aging model calculations is 38 days i.e. the current samples were subjected to 38 fewer days of aging at the worst-case higher temperature in the chambers prior to testing of EPRs.

The accelerated aging model utilizes the Arrhenius equation, which theorizes that the rate of degradation (reaction) in samples doubles ($Q_{10}=2$ per ICH) for every 10°C increase in temperature to determine the real time effect of aging of samples at CRT conditions i.e. the model primarily aims to approximate the impact of high temperature on samples over a period of time. It is recognized in literature that Arrhenius Equation makes theoretical assumptions to predict the shelf life and the actual data need to be analyzed to support the analysis of shelf life of product.

To evaluate the actual impact of EPR performance at higher temperatures over the extended storage period, Hikma performed a detailed data analysis of the accelerated stability samples (40°C / 75 %RH) of three registration/ process validation lots. Data from Initial, 1, 2, 3 and, 6-month testing were analyzed. Individual data (unrounded) points for each EPR were extracted from Hikma's validated LIMS for the purposes of analysis and a summary of the data is available in Stability Report StbDEV001536, located in Section 3.2.P.8.3 of this response.

To study the relationship and variation of EPR results over multiple time points at higher temperature, a Multivariate Regression Analysis method was utilized for the following EPRs: Spray Actuation Content, Spray Content Uniformity, and Actuation Force. These EPRs are amenable to statistical analysis since adequate individual data (n=40) at each time point are available. For the analysis, initial data from finished product release testing (n=10) and supplemental testing data from BOR, MOR & EOR (n=30) were combined to form a sample size of n=40 and represented as a dependent variable in the regression model. Further, for stability data from each time-point, the sample testing data from Upright (n=20) and Inverted (n=20) orientations were combined to form a sample size of n=40 and each time point was represented as the independent variable in the regression model. The data was analyzed using Minitab® Ver 18.1 and the results of the regression analysis are provided in the EPR Data Analysis section under sub-sections A.1 to A.9.

The regression analysis output indicates that the respective EPR results at Initial time point do not correlate to EPR results at 1, 2, 3 and 6 months as indicated by the p-value results that are greater than 0.05 for almost all of the independent variables for all the EPRs. This explains that any variation in EPR results at 1, 2, 3, or 6-month are not associated with variation of EPR results at Initial time point. (Note: a few p-values of independent variables at intermediate timepoints are lower than 0.05 but the p-value for 6-month time point for all EPRs is higher than 0.05 indicating that initial and final time point show no correlation and thus indicating random analytical variability for intermediate time points). Furthermore, the coefficient values of the independent variables noted in the regression equation are consistently low, which indicates that the magnitude of variation in the EPRs results at different timepoints is very small for any variation in the EPR results from the initial timepoint. This implies that the EPR result variations are not significantly dependent on the duration of storage and any variation in results is minor and could be attributed to potential analytical variability. This further demonstrates that there is no significant increase or decrease or attributable trend of Spray Actuation Content, Spray Content Uniformity, and Actuation Force results over the storage period of 6 months at accelerated conditions.

Additionally, for EPR results of Spray Pattern (b) (4) Droplet Size (b) (4) and Plume Geometry, comparative graphs were plotted for comparison and visual interpretation of data from Initial, 1, 2, 3 & 6-month timepoints. For Initial timepoint, testing data from finished product testing was utilized in the graphs. For stability data time points, testing data from Inverted orientation was utilized since it represents the worst-case condition. Bar Graphs were plotted instead of using predicative statistical methods like regression analysis since the number of individual data points for each EPR test at each time point is not adequate to perform statistical analysis that provides meaningful and interpretable results. Comparative graphs are provided below in the EPR Data Analysis section under sub-sections B.1 to B.9. It can be noted from the graphs that each EPR test result compared from initial to 6-month time points show similar results indicating that results over time not only meet the stability specifications but are also comparable. (Note: a few tests show that the results change significantly during intermediate time points but the results during final 6-month and initial time point are comparable indicating random analytical variability for intermediate time points). This further demonstrates that there is no significant increase or decrease or attributable trend of Spray Pattern (b) (4) Droplet Size (b) (4) and Plume Geometry results over the storage period of 6 months at accelerated conditions.

Conclusion: Based on the data analysis performed on accelerated stability samples at 40°C / 75 %RH over 6 months, we conclude that the EPR results are not significantly impacted by higher temperature exposure over an extended duration of time of up to 6-months. Hence, we can use this analysis to support that the additional aging of reliability samples for 38 days (to account for the total storage time to 129 days with CRT 25°C) in stability chambers at 50°C would not significantly impact the EPR results given the low variation of data over multiple time points noted during accelerated stability conditions. Therefore, Hikma deems that the reliability study performed at current accelerated storage conditions and documented in TRCOL001935 can be utilized to continue to support the shelf life of 24 months and to demonstrate combination product EPR performance at 99.99% reliability with 95% confidence.

FDA Response: The sponsor provided adequate accelerated testing for the EPRs (Actuation Force, Spray Actuation Content, Spray Content Uniformity, Spray Pattern, Droplet Size Distribution and Plume Geometry (6 months at 25°C, 60% RH). The sponsor previously performed the reliability study on samples accelerated aged for 3 months. They did not perform additional accelerated aging to support the shelf life of 24 months in the reliability study as requested. However, they performed regression analysis to indicate that EPR result variations are not significantly dependent on the duration of storage. Due to least burdensome, this appears adequate. **Deficiency resolved**

6. In response to Deficiency #23, you have not provided the full data results for each EPR in the process validation testing. You should provide the full test results for each EPR and each lot.

Sponsor Response: Hikma acknowledges the Agency's request to provide full data results for each EPR in the process validation testing. The EPR testing results performed as part of the reliability study on registration/ process validation batch AB0420A are provided in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report which can be found in Section 3.2.P.2 of the application. Attachment F of reliability study report TRCOL001935 provides the individual testing results for all the EPRs tested for reliability study along with the k-value calculations.

Furthermore, three registration/ process validation lots were manufactured to demonstrate successful process transfer from Insys to Hikma (see Table 3); testing results of all EPRs are summarized in TRCOL001055 1927 – Registration / Transfer / Process Performance Qualification Report for Naloxone Nasal Spray, 8 mg which can be found in Section 3.2.P.2 of the application. However, per the Agency's request, individual data points of all EPRs from all three (3) process validation/ registration lots is provided below in Table 4, Table 5, Table 6, Table 7, Table 8, Table 9.

Note that for Actuation Force, Spray Actuation Content, Spray Content Uniformity, at the time of testing, the specification specified 10 samples to align with NDA specification submitted by Insys (1927R-01-01). The specification has since been updated to 20 samples for each test (1927R-01-03) based on FDA IR / CRL correspondences. For every registration/ process validation lot, each test was conducted on 10 composite and 30 throughout-the-run samples, for a total of 40 samples, more than satisfying the 20-sample requirement of 1927R-01-03. Results for all EPRs meet acceptance criteria.

FDA Response: The sponsor provided full data results from the reliability study. This is sufficient. **Deficiency resolved**

Information Request #2 was issued on 3/16/2021. Sponsor provided a response on 3/19/2021.

1. In your additional response to Deficiency #16e, you referenced various journal articles that were reviewed when establishing the actuation force limits. In your summary of the Mathiowetz V articles, you evaluated the mean minus one standard deviation and stated that it represented the worst case of (b) (4).

However, one standard deviation only accounts for 68% of that user population. You should be using two standard deviations to account for 95% of the user population. Therefore, you should modify your maximum individual unit actuation force specification to incorporate two standard deviations from the mean of the pediatric age group as well as from the mean of the adult age group in the journal articles. Additionally, you did not include the standard deviations of the D.V. Doughty article to support the worst case justification. You should provide the two standard deviations from the mean of the D.V. Doughty article to support your specification. You should also provide copies of the journal articles.

Sponsor Response: Hikma acknowledges the Agency's request to modify the maximum individual unit actuation force specification to incorporate two standard deviations (SD) from the mean of the pediatric age group as well as from the mean of the adult age group.

As requested by the Agency, the journal articles previously referenced by Hikma have been provided in this response in Module 3.3. The referenced journal articles were further evaluated taking into consideration the request for two standard deviations. The articles summarized below highlight the worst-case user groups for actuation force that were evaluated.

The actuation force study provided in the journal article (D.V.Doughty et al., Drug Development and Industrial Pharmacy, 2011, 37(2):359–366), determined the mean actuation forces achieved by pediatric participants between the ages of 8–12 years and adult participants between the ages of 18–64 years, were (b) (4) with a SD 1.04 and (b) (4) with a SD 1.40, respectively, with ranges of (b) (4) for pediatrics and (b) (4) for adults. The mean minus 1SD yields a mean actuation force result as follows: (b) (4) for pediatric participants and (b) (4) for adult participants. The mean minus 2SD yields a mean actuation force result as follows: (b) (4) for pediatric participants and (b) (4) for adult participants. Establishing the limit for a maximum individual unit actuation force based on this 2SD approach will merge the maximum limit with average limits and unnecessarily constrict the allowance for any inherent variability of drug product. Furthermore, this study evaluated the participants actuating Flonase® Nasal Spray by vertically holding their thumb on the base of the bottle and their index and middle fingers on the pump flanges. While this study provides ample justification for the achievable actuation force in pediatric and adult participants, the device used in this study is not representative of the device used in the proposed drug product, Naloxone Nasal Spray, 8 mg/Spray.

The actuation force study provided in the journal article (Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6-to 19-year-olds. Am J Occup Ther. 1986 Oct;40(10):705-11. doi: 10.5014/ajot.40.10.705. PMID: 3777107), determined the average performance of normal subjects on the Palmar Pinch grip, which is the same grip utilized to dose the Naloxone Nasal Spray Device. The lowest mean grip strength observed in the intended user adolescents age group (10 to 11 years old) was in the female population utilizing their left hand, requiring a mean actuation force of (b) (4) with a standard deviation (SD) of 2.0. Evaluating the mean minus 1SD, the mean actuation force results to (b) (4). Evaluating the mean minus 2SD, the mean actuation force results to (b) (4).

The actuation force study provided in the journal article (Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985 Feb;66(2):69-74. PMID: 3970660), determined the average performance of normal adult subjects (310 male and 328 female adults, ages 20 to 94) on the Palmar Pinch grip, the same grip utilized to dose the Naloxone Nasal Spray Device. The lowest mean grip strength observed in the intended user adult age group (up to 70 years old) was in the female population, requiring a mean actuation force of (b) (4) with a SD of 3.7 across all females of all ages (20 to 94). Evaluating the mean minus 1SD, the mean actuation force results to (b) (4). Evaluating the mean minus 2SD, the mean actuation force results to (b) (4). As noted above, establishing the limit for maximum individual unit actuation force based on this 2SD approach will merge the maximum limit with average limits and unnecessarily constrict the allowance for any inherent variability in the drug product.

To address the Agency's comments about the actuation force limit covering a majority proportion of the population (95%), Hikma analyzed all the testing results of actuation force from Registration lots (Release and Stability) manufactured at both Hikma and Insys (see excel sheet for lot numbers and data, provided in Section 3.2.P.5.6 of this response). Testing data used for statistical analysis includes Hikma and Insys testing results that represent worst case conditions of storage (5°C, 25°C / 60%RH, 40°C / 75%RH, & 50°C / 75%RH) and shipping / stress conditions (reliability testing). Summary of data analysis and formulas are provided in Table 1 and Table 2 below. Normal Distribution Probability method was utilized to analyze the actual actuation force data and evaluate the probability of generating high values (b) (4) that are outside of the average range of (b) (4) for future samples. It can be noted that the actual mean of actuation force results tested at Hikma is (b) (4) and the actual standard deviation (SD) is low and below 1 ($SD = \frac{(b)(4)}{(4)}$). The Normal Distribution Probability method, which incorporates these low Mean and SD values, indicates that there is a low probability (1.8%) of generating future values outside of the maximum average range of (b) (4) based on the actual testing data. Further, the probability of generating future values at a higher limit of (b) (4) respectively, which is extremely low. Additionally, there is 98.2% probability that future samples will be within the average range of (b) (4).

A histogram plot of the actuation force data (see Figure 1 under data analysis section) also depicts that a majority of the actual testing results are concentrated within the mean range of (b) (4) with a few values above (b) (4) (12 out of 1900) and at the (b) (4) individual limit (5 out of 1900).

Hence, it can be inferred from the data analysis that a majority of devices (98.2%) produced and tested by Hikma are expected to be within the mean range of (b) (4), which aligns with the Agency's request to establish a limit for the majority of the population based on mean-2SD values noted by both journal articles. Probability of occurrence of a few higher values that are greater than (b) (4) and not more than (b) (4) is low (maximum up to 1.8%) but the allowance for higher limit is needed to account for inherent variability associated with the drug product.

Furthermore, the device manufacturer, (b) (4), has established a bridge breaking (actuation force) specification limit of no more than (b) (4). The specification requires that the mean result of 50 units be added to the standard deviation that is multiplied by a constant ($\text{mean} + k \cdot \text{SD}$). This specification allows for individual values to be outside (b) (4) provided the calculated value of 50 units meets the no more than (b) (4) limit. Hikma's maximum allowed actuation force specification for individual units for the drug product utilizes a similar allowance for variability as that of (b) (4) specification. However, Hikma incorporates a testing method that is more conservative in measuring and recording the maximum force needed to either break bridges, pierce the stopper, or start of the spray, as opposed to (b) (4) method, which only measures the force needed to break bridges. This method difference could result in reporting of higher actuation force values, which represent the worst-case for maximum force needed to actuate this device and deliver the full dose.

We also note that (b) (4) has vast experience in producing & supplying the same device components for other customers. Currently the same device is used in seven (7) approved marketed products including Narcan®. Additionally, (b) (4) has noted that they have not logged customer complaints relating to failure or difficulty in actuation of devices.

In conclusion, Hikma deems that the narrowing of the maximum actuation force limit of individual units based on mean-2SD of different population age groups is not feasible since it overlaps with the established mean range of (b) (4). Further, based on the current data analysis, the majority of Hikma's actuation force data is expected to meet the (b) (4) limit, which aligns with the Agency's request to establish a limit for the majority of the population based on mean-2SD values noted in journal articles. Occurrences of high values are expected due to drug product variability, but they are rare and represent a

small proportion of data. Hence, the current data and established specification of mean of 20 units is (b) (4) and no individual units > (b) (4) ensures that majority of users can successfully actuate the devices as intended for its use. See sponsor's response for Data Analysis Section with graphs.

FDA Response: The sponsor's validation is still inadequate. The articles referenced to not validate the upper limit of the specification (b) (4). They reference 7 approved products that are similar but did not provide the actuation force of an assessment of complaints associated with those products. See IR#2.

Information Request #3 was issued on 3/23/2021. Sponsor provided a response on 3/25/2021.

1. You have not provided adequate rationale to support the validation of your actuation force upper limit that no individual unit shall be greater than 5 kg. The clinical articles referenced do not validate the upper limit as each article provides a different value for two standard deviations from the mean. Additionally, you reference that the same device is used in 7 approved products, but you have not provided the actuation force specifications for those products or an assessment of complaints associated with those products. Since this is an emergency-use product, it is especially important that you provide adequate validation to support that the user population is capable of using the device at the upper limit of the actuation force specification. Therefore, it is recommended that you revise your actuation force specification from (b) (4) with no individual unit greater than (b) (4) to only include one upper limit specification that can be sufficiently validated.

Sponsor Response: Hikma acknowledges the Agency's request to include one upper limit specification for actuation force and its validation with adequate rationale.

To establish justification for an upper limit of actuation force, Hikma further evaluated the research article from Mathiowetz et al. that presents the hand strength data needed for palmar pinch actuation action collected as pinch strength measurements from different sub-groups of age. Additionally, actuation force data from Doughty et al. was also evaluated but the sample size of participants for adults and pediatric (n= 20) was not suitable for meaningful data analysis when compared to the large sample size (n = 976) presented in the article from Mathiowetz et al. The palmar pinch test closely represents the actuation action needed for the Naloxone Nasal Spray 8 mg / spray unit dose device and the pinch strength data is generated from a standard test method using a dynamometer.

In the previous IR response, the article from Mathiowetz et al included pinch strength data for children to adolescents i.e. sub-groups of population between 6 to 19-year old males and females. Upon further research, Hikma was able to obtain an additional article from Mathiowetz et al. (submitted with this IR response in Module 3.3) that contains pinch strength data for the adult population for 20 to 75+ year old males and females. Hence, Hikma compiled a complete data set of pinch strength needed for the palmar pinch actuation action for the 10 to 75+ population age group of males and females, which represent the typical age group of users who could be using this device. Hikma's Human Factor study also included participants who were 10 years and above and all participants were able to successfully actuate the device (refer to TRCOL000921, included in Module 1.14.1.4 of the resubmission dated October 29, 2020).

Both articles from Mathiowetz et al. present the summary data for palmar pinch force measured from both the right-hand and left-hand of each participant. In the study, the number of the participants who were right-handed (dominant hand) were larger than the participants who were left-handed. However, Hikma presented and analyzed palmar pinch force data from left hand actuations to represent the worst-case of achievable actuation force by typical users. Data in Mathiowetz et al. articles are presented in pounds unit of measure. Hikma converted the results to kg of force to align with our actuation force unit of measure in the drug product specification. The summary data of actuation force results are presented in Table 1 and Table 2 in the Data Analysis Section. The MS Excel file with data and formulas are also presented with this IR response in Module 3.2.P.5.6.

As noted in Table 1 and Table 2, the average pinch strength (actuation force) for the palmar pinch action for all age-groups and both males and females are above (b) (4), which is the proposed maximum upper specification limit for Naloxone NS 8 mg/ spray. Further, a 95% lower bound confidence interval limit for each age-group for both males and females is greater than (b) (4) (i.e. even after considering potential sampling errors in all age groups, we can infer that 95% of the minimum actuation force values generated from participants of each sub-group of the population will be at least (b) (4) or above).

Furthermore, the pinch strength (actuation force) data was collectively analyzed for the entire spectrum of age groups for both male and female participants to evaluate the maximum specification limit suitable for the majority (95%) of the population. Note that the individual data points of pinch strength (actuation force) for different sub-groups are not available in the articles in order to calculate a population average and standard deviation needed in the statistical formulas. Hence, a weighted average and weighted standard deviation were calculated based on the sub-group size proportions as a close approximation or representation of the population average and standard deviation.

A probabilistic approach using tolerance-based k value was utilized to determine if the (b) (4) upper limit for actuation force is achievable by a majority (95%) of the population. The tolerance-based k value method is also utilized in the reliability study and details including k-actual formulas and k-theoretical reference values are presented in TRCOL001935 Naloxone Nasal Spray, 8 mg/spray Reliability Preconditioning and Testing Report (submitted in Module 3.2.P.2 of the resubmission dated October 29, 2020). The calculated k-actual value for the population groups of men and women is greater than the theoretical k-value. Hence, we can infer from this calculation that there is 95% confidence that 95% of the population can achieve an actuation force of (b) (4).

The Lower bound confidence interval of the entire population of males and females was also calculated, and it is noted that the minimum actuation force values generated from the majority (95%) of population will be at least (b) (4) or above. Additionally, the mean-2SD results of the population of men and women support the upper limit of (b) (4).

As noted in the previous IR response, the device manufacturer's specification for actuation force (bridge breaking force) also supports the (b) (4) upper limit. The same device is currently used for seven (7) marketed products. Table 3 provides the list of the products. Per Agency's request, Hikma confirmed with (b) (4) that the vendor specification for actuation force (bridge breaking force) of devices used with these seven approved products is the same as the one used for the device in Hikma's Naloxone NS 8mg/ spray. However, the specific actuation force specifications from the manufacturers of these drug products are not available to Hikma for reference. (b) (4) has also confirmed that their Quality group has not received any complaints related to actuation failures or issues from their list of customers who currently use this same device.

To further assess customer complaints, Hikma conducted a search of FDA's public database – MAUDE1 to find device actuation failure related complaints for all the seven products listed in Table 3. No records of actuation failures were found. Hikma also performed a search of FDA's public database – FAERS2 to find any adverse events reported for seven products listed in Table 3. This search was inconclusive since information available in FAERS does not detail the cause of adverse events and its subsequent correlation to device actuation failure. Further, Hikma also performed a search of FDA's public database – MedSun3 to find device actuation failure related complaints. No records of actuation failures were found. This further supports that actuation force requirement of (b) (4) devices (used for Naloxone NS 8 mg/ spray) is not known to have reoccurring issues and is suitable for the majority of the population.

Additionally, Hikma reviewed publicly available and redacted copies of NDA review reports4 from the

Agency for an approved life-saving nasal spray product - BAQSIMI® (glucagon) - nasal powder, which utilizes the palmar pinch actuation action. Although the drug product specification was not available due to redactions, it was noted that clinical and human factor study actuation force data was greater than (b) (4) of force (b) (4). This further validates (b) (4) as a suitable maximum actuation force limit. Therefore, based on the above statistical analysis on worst-case (left hand use) pinch strength data and review of similar devices, Hikma deems that the upper specification limit of (b) (4) for actuation force is justifiable and is suitable for a majority (95%) of population users. Hence, Hikma acknowledges the Agency's request to revise the actuation force specification to include one upper limit specification (NMT (b) (4) for each of the 20 individual units). A revised finished product specification is provided with this IR response in Module 3.2.P.5.1 (1927R-01-04). See response for tables.

FDA Response: The information provided is still insufficient to support that the actuation force is acceptable for pediatric patients. The HF study they reference does not identify if it was conducted with devices that actuated at (b) (4). Therefore, it is not suitable evidence for validation of the actuation force. Additionally, referring to other products is not within the regulatory context of the submission for an NDA. The sponsor would have to verify that the devices have the same indication, patient population and design.

Lastly, the study they rely heavily on (Mathiowetz et Al.) is 35 years old. The data provided does not address 2 SD from the lowest age group (10-11). Per Mathiowetz et Al., 2 SD from the left hand of the 40 girls ages 10-11 (mean = (b) (4), SD = (b) (4)) would be (b) (4). 2 SD from the left hand of the 43 boys ages 10-11 (mean = (b) (4), SD = (b) (4)) would be (b) (4). Even 1 SD from any of the 10-11 year olds with their left hand would not be able to actuate devices at (b) (4). In the sponsor's justification, they take 2 SD from the weighted average of all ages. This literature does not sufficiently validate the (b) (4) specification in pediatrics. Of note, the article states that women (n=26) 75+ using their left hand had a mean actuation of 5.2 kg with 1 SD = 1.2 kg.

We also noted that similar nasal spray files for emergency use (ICC2100037) had a specification of (b) (4) but that was for adults only. Therefore, we need additional information to validate the specification for actuation force for pediatric use. It is recommended that the device is approvable for use by adults but not for use by pediatrics or older adults unless the specification is reduced. The sponsor should lower their actuation force specification to no greater than (b) (4). See IR #4.

The tables below use the data from the two studies being leveraged by the sponsor to support validation of their actuation force specification of (b) (4). The studies were performed using the left hand of all individuals.

- a. Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. Am J Occup Ther. 1986 Oct;40(10):705-11. doi: 10.5014/ajot.40.10.705. PMID: 3777107;
- b. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985 Feb;66(2):69-74. PMID: 3970660), determined the average performance of normal adult subjects (310 male and 328 female adults, ages 20 to 94.

The 5th Percentile was calculated for each age group. Therefore, it was determined that pediatrics and older adults (specifically older women) would not be capable of actuating the device with an actuation force specification of (b) (4).

Age	N - Male	Male (L)- Avg	Male (L)- Std Dev	Lower Bound Confidence Interval (95%)	5th Percentile
10-11	43	(b) (4)			
12-13	34				
14-15	34				
16-17	31				
18-19	33				
20-24	29				
25-29	27				
30-34	27				
35-39	25				
40-44	26				
45-49	28				
50-54	25				
55-59	21				
60-64	22				
65-69	27				
70-74	26				
75+	25				

Age	N- Female	Women (L)- Avg	Women (L)-Std Dev	Lower Bound Confidence Interval (95%)	5th Percentile
10-11	40	(b) (4)			
12-13	36				
14-15	34				
16-17	35				
18-19	30				
20-24	26				
25-29	27				
30-34	26				
35-39	25				
40-44	31				
45-49	25				
50-54	25				
55-59	25				
60-64	25				
65-69	28				
70-74	29				
75+	26				

Information Request #4 was issued on 4/15/2021. The sponsor provided a response on 4/20/2021. The review team, including CDRH and CDER, have reviewed your submission of March 25, 2021 which references the following studies intended to support validation of the actuation force specification of (b) (4) for your product:

- Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. Am J Occup Ther. 1986 Oct;40(10):705-11. doi: 10.5014/ajot.40.10.705. PMID: 3777107;
- Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985 Feb;66(2):69-74. PMID: 3970660), determined the average performance of normal adult subjects (310 male and 328 female adults, ages 20 to 94.

As you have summarized, the reported average pinch strength (actuation force) for the palmar pinch action for all age-groups and both males and females is above (b) (4), with a 95% lower bound confidence interval limit of greater than (b) (4) (Tables 1 and 2 in your submission).

However, we do not consider the average or 95% CI to be the appropriate metric to use. CDRH uses the 5th percentile to be the appropriate metric because it calculates the acceptable actuation force for 95% of each age group. This is a calculation that has been applied to literature and clinical studies for other similar products. Validating the actuation force specification is especially important for your combination product because it is an emergency-use device where the drug will not be delivered if the individual cannot actuate the device. Using these data and the 5th percentile, males 10 to less than 14 years of age and females 10 to less than 16 years of age have a palmar pinch strength of (b) (4). Females 65 to 69 years and over 75 years have palmar pinch strength of less than (b) (4). Therefore, we remain concerned that pediatrics and older adults, especially older women, will not be capable of actuating the device if product is marketed using your proposed actuation force specification of (b) (4).

We acknowledge the 7 products that are marketed with the same device as your product (Table 3). However, there are multiple potential differences that could influence the actuation force specification, including differences in the device (e.g. changes to dimensions, materials or colors) as well as differences in drug products. These 7 products are also not intended to be administered by pediatrics.

Your product, Naloxone Nasal Spray 8 mg/spray is intended for community use in settings of accidental opioid overdose. In this situation, the patient is not administering the product to themselves and another person (e.g., layperson) will be administering the product to the patient. In order to ensure the patient receives sufficient exposure to naloxone to reverse the overdose, your product should be designed such that it can be actuated easily in an emergency setting by a broad range of people.

Therefore, we do not agree that you have provided adequate justification to support a proposed actuation force specification limit of (b) (4). We recommend you reduce your actuation force specification from no greater than (b) (4) to no greater than (b) (4) and submit a revised finished product specification.

Sponsor Response: Hikma acknowledges the Agency's recommendation to lower the specification limit for Actuation Force from no greater than (b) (4) to no greater than (b) (4) for the proposed drug product, Naloxone Nasal Spray, 8 mg/Spray. Hikma has reviewed historical data and has adopted the FDA recommendation for the specification of NMT (b) (4). The analytical procedure and historical results were further reviewed as part of this change.

The actuation force is captured during spray content uniformity analysis utilizing a (b) (4) (b) (4) Actuator and processed through (b) (4) Software in unit dose mode. The release of the drug product from the device can be visually observed in graphs generated during the analysis, however the exact point in which the spray is released from the device occurs within milliseconds (ms). To correlate the actuation force and the release of the drug product from the device, the plume geometry data was further evaluated.

The plume geometry analysis utilizes the same the (b) (4) (b) (4) Actuator and (b) (4) Software in junction with the (b) (4) instrumentation. The plume geometry report contains the image of the spray, the actuation graph and the intensity graph, please refer to Figure 1 for an example. The release of the drug product from the device is captured by a camera during the plume geometry analysis in the (b) (4) Software. The video playback of the captured spray can be analyzed through the software to determine the exact time in which the drug product is released from the device and the actuation force at the time of release.

Hikma evaluated the plume geometry data of all three registration lots manufactured at West-Ward Columbus Inc. (WWCI) from the 6-month stability time point, stored at 40°C/75% RH (relative humidity) in the inverted position. The data showed that the start of the spray of the drug

product from the device occurs much earlier; the start of the spray occurs at approximately (b) (4) and the end of the spray starts at approximately (b) (4). An example of the extracted data from the plume geometry analysis in which the start of the spray is seen in the video and the correlating graphs is presented in Figure 2.

From this data, it was concluded that the start of spray needed to be clarified in the analytical procedure (1927-02). The measured actuation force has historically been reported as the greatest force value been taken from the three points as per the graph in the current analytical procedure, Figure 3. The analytical procedure has been updated to reflect the corrected graph as presented in Figure 4. As part of this change, it has been determined that most appropriate measuring point for actuation force is the initial point of the bridge break, wherein the user experiences the force required to initiate the spray sequence.

It is important to understand the relationship between the bridge breaking force and maximum force as it relates to the user experience. The most important force that the user must exert to actuate the device is the bridge breaking force (triggering force). This is because the system is static until the user exerts enough force to break the bridges which allows the system to be set in motion. After the bridge breaking force is achieved and the bridges are broken, the user has the benefit of momentum for the remainder of the actuation. Although subsequent forces in the actuation profile may sometimes be greater than that of the bridge breaking force (triggering force), the user does not individually exert greater force at these stages because they have the benefit of momentum generated by exceeding the triggering force.

With this modification, the analytical procedure is further aligned with (b) (4) methodology. Hikma has updated the analytical procedure to measure actuation force at the bridge breaking (A), corresponding the max force at rest required by the user population (user actuating the device), which supports the (b) (4) upper limit.

Hikma acknowledges the Agency's request to revise the actuation force specification to tighten the upper limit specification (NMT (b) (4) for each of the 20 individual units). A revised finished product specification is provided with this IR response in Module 3.2.P.5.1 (1927R-01-05) and a revised analytical procedure for actuation force is provided with this IR response in Module 3.2.P.5.2 (1927-02-03). See the IR response for the complete graphs.

FDA Response: The sponsor agreeing to reduce the actuation force to no greater than (b) (4) is acceptable. However, we have additional concerns over the validation of the actuation force methods and how they calculate the actuation force. See IR #5.

Information Request #5 was issued on 4/21/2021. The sponsor provided a response on 4/23/2021.

1. In response to IR#4, you reduced the actuation force specification to no greater than (b) (4). You also changed the actuation force test methods following the change in specification. This raises concerns over whether the actuation force methods are adequately validated. Additionally, you claim that video playback of the captured spray during plume geometry analysis is analyzed through software to determine the exact time in which the drug product is released from the device and the actuation force at the time of release. You also claim that the force of the fluid breaking the bridge of the device (point A from Figure 4 provided in your IR#4 response) is the actuation force. However, actuation force is the force required by the user to depress the plunger to initiate the spray and deliver the dose. We have concerns over whether the forces in Figure 4 represent the actuation force. It is unclear how you determined that the force of the fluid breaking the bridge is equivalent to the force required to depress the plunger for actuation.

Clarify how the force of the fluid breaking the bridge is equivalent to the force required to depress the plunger and deliver the full dose.

Provide an explanation of how you validated your new proposed actuation force methods and include graphs that clearly indicate the data collection. Alternatively, re-perform the actuation force testing using a system to measure the force required to depress the plunger to deliver the full dose and validate all test methods.

Sponsor Response: In response to the FDA information request received on April 21st, 2021, Hikma would like to clarify that the method to measure actuation force has not been changed but rather updated to indicate that the measurement of the force at point A is the critical force required to break the bridge and ensure the delivery of the dose to the patient. Therefore, no additional method validation is required.

Additionally, Hikma would like to explain the rationale for targeting the bridge breaking point on the actuation profile as the measured actuation force. Specifically, it is important to understand the relationship between the unit dose delivery system (device) and the actuation force. A diagram of the unit dose delivery system used for the proposed drug product, Naloxone Nasal Spray 8 mg/spray, is provided in Figure 1. The Naloxone Nasal Spray formulation is filled in a clear glass vial, stoppered with a plunger, and fitted within the unit dose delivery system. The dose is delivered by the user gripping the device with their thumb on the bottom of the container holder, and their index and middle fingers on the top of the shoulders of the device. The user will actuate the device using a Palmer Pinch grip. The user will firmly press up with their thumb on the bottom of the container holder while firmly pressing down with their index and middle fingers on the top of the shoulders of the device. As the user pinches the device, the bridges holding the container holder in place are broken, then (b) (4) pierces the stopper, and the dose is delivered via a continuous spray. The force at rest (point of bridge break) is the initial threshold force, which is the most important force the user will exert in actuating the device; the subsequent dose is continuously delivered by the force in motion. For additional details on the device operation sequence refer to Figure 2.

As discussed in Hikma's previous response to IR #4, the critical force that the user must exert to actuate the device is the bridge breaking force (triggering force). This is because the system is static (at rest) until the user exerts enough force (force at rest) to break the bridges which allows the system (device actuation) to be set in motion. After the user exerts enough force (force at rest) to break the bridges (point A, in Figure 3), the user has the benefit of momentum (force in motion) for the remainder of the actuation (points B, C, and D, in Figure 3). Furthermore, the time delay from breaking bridges (point A, in Figure 3) to reaching the end of dose delivery (point D, in Figure 3) is extremely brief (approx. (b) (4)) and any small high or low variations in the required force in the interim between points A and D can be countered by the benefit of achieved momentum during the actuation. Hence, Hikma deems that measuring the actuation force at point A (bridge breaking force) is more representative of the actual force required to deliver the full dose.

Hikma further clarifies that the analytical procedure provided in the previous IR response, 1927-02-03, is not a new proposed actuation force method; it is the same method as previously filed but updated to provide clarity to the identification of the critical actuation force position (point A, in Figure 3) and the subsequent position changes (points B, C, and D, in Figure 3) on the actuation force graph. The actuation parameters and collection of raw data remain unchanged.

In conclusion, the critical force required to ensure the delivery of the dose to the patient is the force required to break the bridge (point A, in Figure 3). The analytical procedure was revised to provide clarity to the analyst that the bridge breaking position on the actuation force profile is the appropriate measurement location for actuation force. As there are no modifications made on the execution steps of the analytical procedure, no additional validation is necessary.

FDA Response: The sponsor's approach for determining the actuation force appears reasonable as long as they include methods in their release testing procedures/test method on what to do if they find that force 'B' or 'C' are higher than point 'A' and the actuation force does not meet the (b) (4) force specification. This will be conveyed to the sponsor in IR#6.

Information Request #6 was issued on 4/23/2021. The sponsor provided a response on 4/26/2021.

1. In response to the information request #5, dated April 21, 2021, you provided justification for how the actuation force is determined. We agree with the proposed definitions for 'A', 'B', 'C' and 'D' (Figure 3). However, it is unclear what steps would be taken during release testing in the instances where forces 'B' or 'C'- 'D' are higher than the actuation force 'A' in the event of future manufacturing issues/defects. If the forces at 'B' and 'C'- 'D' are higher than (b) (4) then the user may receive an incomplete dose. Therefore, update your method with instructions on how to analyze each feature of your curve ('A', 'B', 'C'- 'D') independently to ensure the forces are below (b) (4) and capture any potentially defective product.

Sponsor Response: Hikma acknowledges the Agency's request to ensure the forces (Points A, B, C, and D) are below (b) (4). However, Hikma has determined that forces at Points B, C, and D are not Critical Quality Attributes due to the forces varying up or down based on differences within user populations (i.e., velocity and applied force). Based on this, an actuation force value above (b) (4) for Points B, C, and D is not meaningful to determine device defects that will prevent a full dose of drug to be administered, as further discussed and supported below.

The most appropriate way to measure system performance is to apply a constant velocity and measure the resulting force. This standard is consistent across many industries. However, users tend to apply a constant force more so than a constant velocity because human muscles apply force as a primary function and require training to learn to meter force and control velocity, both of which require feedback loops. As a result, system modes of operation that are highly rate dependent will not necessarily correlate to human capability when measured using a constant velocity. Point C through Point D on the actuation force curve (see Figure 1) is the hydraulic portion of the curve representing the fluid being pushed through the exit orifice on the nozzle. The force measured from Point C through Point D is proportional to actuation velocity squared and is therefore highly rate dependent.

To demonstrate the actuation force profile at A, B, C and D in relation to the complete dose delivery, Hikma performed additional development studies. The experimental details of development studies are as follows:

The actuation force is captured during spray content uniformity analysis utilizing a (b) (4) (b) (4) Actuator and processed through (b) (4) Software in unit dose mode. The following (b) (4) Actuator Parameters are used for evaluating the actuation of Naloxone Nasal Spray 8 mg/spray:

Parameter	Setting
Actuation Velocity	(b) (4)
Initial Delay	
Hold Time	
Contact Force	
End of Stroke Force	

Hikma performed multiple development studies to demonstrate that point A is the critical point to measure for actuation force and that controlling the forces at Points B, C, and D are not necessary to determine the quality of the drug product. Modifications were made to the actuation parameters to determine the impact of the force at Point A (bridge breaking) and Point D (end of spray) on the actuation profile and the resulting impact on the ability to deliver full intended dose.

The first parameter modified was the actuation velocity, which is the maximum velocity achieved during the actuation stroke. The actuation stroke is the movement of the actuator from the Contact Force Position to the End of Stroke Force Position, as depicted in Figure 5, images (b) and (c), respectively. The actuation velocity was modified in two separate stages: 1) lowered from (b) (4) and 2) increased from (b) (4) to demonstrate the rate dependence from the start of spray through end of spray (point C through point D), which is the fluid flow through an orifice. Incompressible flow through an orifice from the start of spray through end of spray (point C through point D) should demonstrate rate dependence between actuation velocity and actuation force. However, shear failure to break the bridges (Point A) should not demonstrate rate dependence. In addition, the Spray Actuation Content was collected to demonstrate that the entire dose was delivered from each device evaluated.

To ensure the study was representative of a sample at the end of shelf life, the following sample was used throughout this study: Hikma lot number AB0419A stored at accelerated conditions (40°C/75% RH, Inverted) for 6 months. From this study, it is concluded that the actuation velocity directly impacts the actuation force at the end of spray (Point D) based on the shift observed in the actuation force values at Point D. However, the actuation force required to break the bridges (Point A) demonstrated no rate dependence as the results were unchanged. As the actuation velocity is increased to (b) (4) the actuation force profile at Point A is unchanged, but from the start of spray through the end of spray (Point C and Point D) increases with velocity. As the actuation velocity is decreased to (b) (4) the actuation force profile at Point A is unchanged but the start of spray through the end of spray (Point C and Point D) decreases.

As noted above, in addition to the actuation force, the Spray Actuation Content values were collected in tandem during this study to ensure a complete dose can be delivered at a higher and lower velocity. From the data generated (see Table 1, Table 2, and Table 3), it can be noted that the complete dose is delivered at each velocity studied, demonstrating conclusively that reducing the force applied in the C and D regions (and resulting velocity) has no impact on dose delivery. This further confirms that Point A on the actuation force profile is the critical point to measure for actuation force. Please refer to Tables 1 - 3 and Figures 2 - 4 for the results from the actuation velocity study. Please refer to Appendix 1- 6 for examples of the Actuation Force Reports from each variable studied containing the actuation force profile from the actuation velocity study.

The second parameter modified was the end of stroke force, which is the point at which the actuator device ends the actuation stroke, refer to Figure 5 for (b) (4) provided diagrams. The end of stroke force was lowered from (b) (4) to mimic the actuation force specification limit, and a point below the actuation force specification limit. Ten devices from an expired sample, Insys lot 10701218 (20% ethanol formulation), were evaluated at lower end of stroke forces, (b) (4). The data generated was then compared to the nominal data

previously generated at end of shelf life (24 months, 25°C/60% RH). From this study, it is concluded that even if the maximum force applied at or by the end of spray is maintained at (b) (4) the full dose is delivered. We can infer from this data that even if a user can only achieve a maximum actuation force of (b) (4) by the end of actuation stroke then the dose is still fully delivered, as the spray intensity graph for each device was unchanged. Actuation Point A remains unchanged as would be expected, supporting Point A as the appropriate control for the Actuation Force test. Please refer Appendix 7- 9 for examples of the Plume Geometry Reports from each variable studied containing the actuation force profile and intensity graph from the end of stroke force study.

Details of the experiments and the results are provided in the sections above are summarized in the table below for ease of review:

Description of Development Study	Position on Actuation Force Profile	Description of Position on Actuation Force Profile	Observation as each Point on Actuation Force Profile	Conclusion
Study 1: Actuation Velocity The actuation velocity was lowered (b) (4)	A	Force to break the bridges	The actuation force required to break the bridges was unchanged with changes to the actuation velocity.	From this study, it is concluded that the actuation velocity directly impacts the actuation force at the end of spray (Point D) based on the shift observed in the actuation force values at Point D. This data supports that complete dose delivery is achieved at forces as low as (b) (4) force at point D. This study also illustrates that the actuation force required to break the bridges (Point A) demonstrated no rate dependence as the results were unchanged. These results confirm that Point A on the actuation force profile is the critical point to measure for actuation force and the appropriate Critical Quality Attribute for the test.
	B	Force to pierce the stopper	Similar or lower than Point A.	
	C	Start of the spray	Lower than Point A.	
	D	End of the spray	Increase in actuation velocity from (b) (4) increased the mean force at point D from (b) (4) (b) (4) Mean Shift is observed with changes to the actuation velocity. However, complete dose can be delivered with (b) (4) test speed). Therefore, there are no concerns on the complete delivery of dose.	
Study 2: End of Stroke Force The end of stroke force was lowered (b) (4)	A	Force to break the bridges	Is critical for actuation of the device.	From this study, it is concluded that after bridges are broken, the complete dose can be delivered even with a force as low as (b) (4) This study further supports that the actuation force specification limit of (b) (4) at Point A is the critical control for the device actuation and delivery of a full dose.
	B	Force to pierce the stopper	Similar or lower than Point A.	
	C	Start of the spray	Lower than Point A.	
	D	End of the spray	The full dose was delivered from the device utilizing a force even a (b) (4)	

Note: The above experiential testing with modified parameters was performed one-time only to support our study objectives. The current actuation force testing method for routine testing remains unchanged.

Based on these findings, it can be concluded that if the user has sufficient strength to overcome the bridges, the user can complete dose delivery. Therefore, a (b) (4) limit on point A will effectively control product quality and ensure consistent dose delivery.

To address the Agency's concern regarding future manufacturing defects and/or the potential for the user to receive an incomplete dose, the actuation force is measured alongside the spray actuation content (SAC) and spray content uniformity (SCU). If a significantly high actuation force driven by any of the points after Point A were to occur, the spray actuation content and spray content uniformity of that device would be evaluated for the same device in

tandem. This ensures that if a significant force is required to actuate, the spray actuation content value of the device would confirm the dose load, full, partial, or no dose. Additionally, the analytical procedure contains an example of the actuation profile for the drug product; if an aberrant result was generated, the analyst would detect the defect immediately and investigate the result.

In conclusion, the data provided from the development supports that Point A is the Critical Quality Attribute and actuation forces of higher or lower than (b) (4) after the initial bridge breaking actuation force (Point A) would result in full dose delivery. Therefore, revisions to the method to include additional controls for Points B, C and D are not needed as these values do not represent Critical Quality Attributes. Furthermore, controls for product delivery / defects are also assessed through testing for Spray Actuation Content and Spray Content Uniformity in tandem on the same device, thereby ensuring that potential dose delivery defects will be appropriately identified and investigated. Accordingly, the current product control strategy ensures that defects are properly managed and that the patient will receive the intended dosage of the product. See IR response for additional graphs and Appendix 1- 9, including Actuation Force Result tables at various actuation velocities.

FDA Response: The sponsor did not update their test methods with instructions on how to analyze each feature of your curve ('A', 'B', 'C'- 'D') independently to ensure the forces are below (b) (4) and capture any potentially defective product. They claim that Points B, C, and D are not Critical Quality Attributes and are not meaningful to determine device defects. Alternatively, the analytical procedure contains an example of the actuation profile for the drug product; if an aberrant result was generated, the analyst would detect the defect immediately and investigate the result.

They state in their methods that if a significantly high actuation force driven by any of the points after Point A were to occur, the spray actuation content value of the device would confirm the dose load, full, partial, or no dose. We do not believe this is a suitable method to detect manufacturing failures that affect actuation force. Additionally, their method does not specify what they would consider an aberrant result. We consider an aberrant result anything > (b) (4) and therefore, we reiterate our IR#6 that they should update their method with instructions on how to analyze each feature of your curve ('A', 'B', 'C'- 'D') independently to ensure the forces are below (b) (4) and capture any potentially defective product. See Teleconference

Teleconference held on 4/27/2021: A teleconference was held on 4/27/2021 with the sponsor to state the concerns listed above in FDA Response to IR#6 and to provide clarification on CDRH's stance. FDA requested that the sponsor update their methods to initiate an investigation if any point on the graph between B through D is over (b) (4). The sponsor agreed to provide an amended protocol. They will be revising their methodology to include that if any point between B and D (including C) are over (b) (4), they will initiate an investigation. This is in addition to the sponsor's original plan to provide an example curve to the analyst to detect any additional aberrant results (e.g. a very unusual curve that is under (b) (4)). This deficiency is resolved and the overall device component is acceptable.

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/

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

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

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

Date of This Review:	April 1, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 212045
Product Type:	Combination Product
Drug Constituent Name and Strength	naloxone hydrochloride nasal spray, 8 mg
Device Constituent:	Nasal Spray
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hikma Pharmaceuticals USA INC (Hikma)
Submission Date:	10/29/20; 1/29/21; 2/17/21
OSE RCM #:	2019-944, 2019-943
DMEPA Safety Evaluator:	Zahra Farshneshani, PharmD
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Deputy Director	Irene Z. Chan, PharmD, BCPS

1. REASON FOR REVIEW

We reviewed the human factors (HF) validation study results report and labels and labeling submitted on October 29, 2020 under a Class 2 resubmission for NDA 212045 for naloxone hydrochloride nasal spray 8 mg. This is a combination product with a proposed nasal spray device constituent part that is intended for the emergency treatment of known or suspected opioid overdose for adult and pediatric patients.

1.1 PRODUCT DESCRIPTION

The product is a nasal spray with the device containing naloxone HCl 8 mg. The device is housed in a blister card and packaged with two blister cards per box. There is a “Quick Instruction Sheet” attached to the bottom of each blister card. Please see Appendix E for a link to the images.

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

We reviewed the HF validation study results report under IND 134954 on February 12, 2019, and we provided recommendations in an Advice Letter dated April 26, 2019.^a Due to methodology concerns, we recommended that the applicant conduct a new HF validation study to support their marketing application, and we also recommended they submit their HF validation study protocol for Agency review before commencing the study.

NDA 212045 was submitted on April 30, 2019 and the submission included a use-related risk analysis (URRA) and the previously submitted HF validation study results report (the same results report submitted under IND 134954). During the NDA review cycle, the applicant submitted an HF validation study protocol for Agency review under IND 134954, and we provided HF validation study protocol recommendations.^b NDA 212045 received a complete response (CR) on February 28, 2020 due to deficiencies from CMC, Nonclinical, CDRH, and Human Factors. In the CR letter, the HF deficiency stated that there was insufficient data or information to support the design of the proposed user interface, and we requested that Hikma update the product’s user interface and use-related risk analysis (URRA) and submit the results of their HF validation study.^c

^a Chan, I. Human Factors Validation Study Protocol - Advice for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 26. RCM No.: 2019-367.

^b Chan, I. Human Factors Validation Study Protocol - Advice for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 09. RCM No.: 2019-367-1.

^c Truong, S. Complete Response. Silver Spring (MD): FDA, CDER, OND, DAAP (US); 2020 February 28. NDA 212045.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product. We also address the labels and labeling in section 3.3.

3.1 SUMMARY OF STUDY DESIGN

We previously reviewed the HF validation study protocol and note that our recommendations were implemented.^d We find the study is methodology acceptable.

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	This study enrolled thirty subjects: 15 adults with normal literacy levels and adults with low-literacy levels (based on a reading level test), and 15 adolescents aged 12 to 17.
Training	No training was provided.
Test Environment	The test environment was designed to replicate a potential opioid overdose situation. The subject entered a loud room to find a mannequin in a slumped or prone position. Next to the overdosed “person” was a box of Naloxone containing two devices, each in a separate blister card.
Simulated Use Session Structure	• The subject will be told the mannequin is a proxy for a person who has overdosed, and the mannequin is to be given the Naloxone. No instructions will be given to the subject other than to enter the room and use the Naloxone on the mannequin. The users will proceed with interacting with the product as they normally would in real-world use. • Interview • Root Cause Analysis

3.2 RESULTS AND ANALYSES

Table 3 describes the study results associated with one critical task that required additional investigation to inform the residual risk consideration. The table also

^d Flint, J. Human Factors Study Report and Labels and Labeling Review for Naloxone Nasal Spray. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 26. RCM No.: 2019-367.

includes Hikma Pharmaceuticals USA INC's analyses of the results, and DMEPA's analyses and recommendations.

Table 3: Summary and Analyses of Study Results-Critical Task

Tasks Evaluated (C for Critical and E for Essential)	Number and Description of Use Errors	Number and Description of Close Calls and Use Difficulties	Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Administering another dose using a new unit (if needed) [C]* *The Applicant considered this task non-critical; however, we consider this task to be critical because failure to complete this task or completing it incorrectly may result in delay of therapy and risk of patient harm.	6 participants did not administer a second dose.	None	Subject IDs (b) (6) did not give the second dose. Their subjective feedback indicated the following: • (b) (6) – did not know you had to • (b) (6) – only read up until “call for help” on the directions • (b) (6) – picture said one nostril and did not think it was clear to do second nostril • (b) (6) – it said insert into one nostril but mention of second dose is not as clear • (b) (6) – didn’t read any instructions; only saw the front of the box	The Applicant’s RCA included the following assessment of participant performance: • Mental disconnect (inability to understand the instructions) - o 1 subject noted the picture said one nostril and that it did not make it clear to do a second nostril - o 1 subject said it says insert into one nostril but the mention of second dose is not as clear • Environmental hinderance (stressed caused by urgency of situation)	No mitigation strategies offered. The Applicant found the residual risk acceptable.	The Applicant’s URRAs indicated that failure to administer another dose using a new unit (if needed) might result in a delay of therapy. Our review of the study results identified subjective feedback from two participants indicating confusion with the labeling as they stated that the picture and/or instructions were not clear. The study participants were confused by the graphic and the instructions indicating “one nostril”. Our review of the labeling finds that the step 3 includes instructions regarding administration of another dose using a new unit. We note that the phrase “give another dose.” is used twice in step 3 and is highlighted in a different color font to increase prominence. Additionally, we were concerned that the packaging of the product may have contributed to confusion. Thus, we sent an Information Request to

Table 3: Summary and Analyses of Study Results-Critical Task

Tasks Evaluated (C for Critical and E for Essential)	Number and Description of Use Errors	Number and Description of Close Calls and Use Difficulties	Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
			• (b) (6) – did not notice the second dose in the box	- o 1 subject only read up to “call for help” on the instructions - o 1 subject did not read the instructions at all and only saw the front of the box - o 1 subject did not notice the second dose in the box • Artificial environment (being in a simulated situation) - o 1 subject did not know they had to do both doses during the testing simulation		request the Applicant provide additional images of the proposed product packaging for Agency review to assist us in determining whether the second nasal spray is visible. On January 29, 2021, the applicant provided a response to our Information Request and provided images of how the product is packaged. We did not identify any issues with the product packaging. Based on the overall assessment of the study results and labels and labeling, we find the residual risk acceptable and have no recommendations at this time.

ANALYSIS OF CRITICAL TASKS

In addition to the critical task discussed in Table 3 above, we observed use errors/close calls/use difficulties with five additional critical tasks. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis and Applicant's proposed risk mitigation strategy to determine acceptability. We determined the residual risk is acceptable and we have no further recommendations:

- Identifying the overdose (checking for response)
- Tilting head back and supporting neck
- Moving person to a recovery position after administering the dose
- Waiting 2 to 3 minutes to assess the effectiveness of the first dose
- Calling 911

3.3 LABELS AND LABELING

Table 4 below includes the identified medication error issues with the submitted packaging, label and labeling, and instructions for use our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 4: Identified Issues and Recommendations for HIKMA PHARMACEUTICALS USA INC (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Container Label(s) and Carton Label			
1.	The container labels and carton labeling do not include the location of the lot number.	The lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Add the lot number to the container label and carton labeling.
2.	The container labels and carton labeling do not include the expiration date.	The expiration date is required on the immediate container and carton labeling in accordance with 21 CFR 211.137.	Add the expiration date to the container labels and carton labeling. Furthermore, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format

			if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.
Carton Labeling			
1.	The product identifier is missing.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. ^e The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

^e Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

4. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrate that representative users can use the product safely and effectively. Our evaluation of the proposed packaging, label and labeling, prescribing information and instructions for use identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for Hikma Pharmaceuticals USA INC. We ask that the Division convey Table 3 in its entirety to Hikma Pharmaceuticals USA INC so that recommendations are implemented prior to approval of this NDA 212045. We determined our recommendation can be implemented without submission of additional HF validation study data in this instance.

4.1 RECOMMENDATIONS FOR HIKMA PHARMACEUTICALS USA INC

We found the results of your human factors (HF) validation study acceptable. Our evaluation of the proposed packaging, label and labeling, prescribing information and instructions for use identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3 and we recommend that you implement these recommendations for this NDA 212045. In this particular instance, we determined the recommendations can be implemented without submission of additional HF validation study data.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for naloxone that HIKMA PHARMACEUTICALS USA INC submitted on 2/8/2021.

Table 4. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Opioid antagonist
Active Ingredient (Drug or Biologic)	Naloxone HCl
Indication	Opioid overdose
Route of Administration	Intranasal
Dosage Form	Intranasal Spray
Strength	8 mg
Dose and Frequency	<u>Initial Dosing</u> The recommended initial dose of Kloxxado nasal spray in adult and pediatric patients is one spray delivered by intranasal administration into one nostril, which delivers 8 mg of naloxone hydrochloride to adult or pediatric patients. <u>Repeat Dosing</u> Seek emergency medical assistance as soon as possible, after administering the first dose of Kloxxado nasal spray. If the desired response is not obtained after 2 or 3 minutes, administer an additional dose using a new Kloxxado nasal spray in alternate nostrils with each dose. If there is still no response and additional doses are available, administer additional doses of Kloxxado nasal spray every 2 to 3 minutes using a new Kloxxado nasal spray until emergency medical assistance arrives. The requirement for repeat doses of Kloxxado nasal spray depends upon the amount, type, and route of administration of the opioid being antagonized.

	If the patient responds to Kloxxado nasal spray and subsequently relapses back into respiratory depression before emergency assistance arrives, administer an additional dose using a new Kloxxado nasal spray, in the opposite nostril, and continue surveillance of the patient. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance. Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and require repeated administration of Kloxxado using a new nasal spray [see <i>Warnings and Precautions (5.2)</i>]
How Supplied	Blister Packaging
Storage	Room Temperature
Container Closure/Device Constituent	(b) (4) Intranasal Device
Intended Users	Lay Users
Intended Use Environment	Any environment

APPENDIX B. BACKGROUND INFORMATION

B. PREVIOUS HF REVIEWS

On January 27, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, naloxone or NDA 212045 or IND 134954. Our search identified two previous reviews^{f,g,h,i,j,k}, and we considered our previous recommendations to see if they are applicable for this current review and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The use related risk analysis can be accessible in EDR via:

<\\CDSESUB1\evsprod\nda212045\0026\m1\us\insys-user-risk-analysis.pdf>

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

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

<\\CDSESUB1\evsprod\nda212045\0026\m1\us\insys-hf-study-ins018-2-16.pdf>

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

We issued an Information request to obtain formative studies and pictures of how the product is packaged. The Applicant response addressed our concern,

Th response is accessible via EDR: <\\CDSESUB1\evsprod\nda212045\0026\m1\us\questions-responses.pdf>

We issued an Information Request to obtain the rationale for submitting different labeling than what was used in the HF study. We also asked for changes in the protocol since our last review.

^f Flint, J. Human Factors Study Report and Labels and Labeling Review for Naloxone Nasal Spray. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 26. RCM No.: 2019-367.

^g Flint, J. Human Factors Validation Study Protocol Review for Naloxone Nasal Spray. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 07. RCM No.: 2019-367

^h Chan, I. Human Factors Validation Study Protocol - Advice for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 26. RCM No.: 2019-367.

ⁱ Chan, I. Human Factors Validation Study Protocol - Advice for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 26. RCM No.: 2019-367.

^j Mathew, D. Memorandum of Teleconference for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, PMS (US); 2019 Apr 17.

^k Chan, I. Human Factors Validation Study Protocol - Advice for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 09. RCM No.: 2019-367-1.

The response is accessible via EDR: <\\CDSESUB1\evsprod\nda212045\0029\m1\us\questions-responses-to-fda-letter-20210211.pdf>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels, Labeling and Packaging Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following naloxone hydrochloride labels and labeling submitted by Hikma Pharmaceuticals.

- Container label received on February 8, 2021
- Carton labeling received on February 8, 2021
- Blister labeling received on February 8, 2021
- Instructions for Use received on February 8, 2021
- Carton Packaging received on January 29, 2021
- Prescribing Information (Image not shown) received on February 8, 2021 available from: <\\CDSESUB1\evsprod\nda212045\0027\m1\us\spl-naloxone-ns-kloxxado-c50001066-01-k01-pdf.pdf>

F.2 Label and Labeling Images

Container label



2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

PATIENT LABELING REVIEW

Date: March 23, 2021

To: Joyce Chin, PharmD
Regulatory Health 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)

Sharon R. Mills, BSN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nima Ossareh, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

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

Dosage Form and Route: nasal spray, for intranasal use

Application Type/Number: NDA 212045

Applicant: Hikma Pharmaceuticals USA, Inc.

1 INTRODUCTION

On October 29, 2020, Hikma Pharmaceuticals USA, Inc. submitted for the Agency's review a resubmission to their original New Drug Application (NDA) 212045 for TRADENAME (naloxone hydrochloride) nasal spray. This resubmission is in response to a Complete Response Letter received from the Agency on February 28, 2020. The proposed indication for TRADENAME (naloxone hydrochloride) nasal spray is for the emergency treatment of known or suspected opioid overdose.

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 November 19, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) 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 will be forthcoming.

2 MATERIAL REVIEWED

- Draft TRADENAME (naloxone hydrochloride) nasal spray PPI and IFU received on October 29, 2020, and received by DMPP and OPDP on March 8, 2021.
- Draft TRADENAME (naloxone hydrochloride) nasal spray Prescribing Information (PI) received on October 29, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 8, 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.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU 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 and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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

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

Memorandum

Date: 3/23/2021

To: Jungwon Chin, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Nima Ossareh, PharmD, RAC Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for (b) (4) (naloxone hydrochloride) nasal spray

NDA: 212045

In response to DAAAP consult request dated November 19, 2020, OPDP has reviewed the proposed product labeling (PI) for (b) (4) (naloxone hydrochloride) nasal spray.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on March 8, 2021, and are provided below.

PPI, IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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MEMORANDUM
HUMAN FACTORS ADVICE

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

Date of This Memorandum:	02/14/2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 212045
Product Name and Strength:	Naloxone hydrochloride nasal spray, 8 mg
Applicant/Sponsor Name:	Hikma Pharmaceuticals
OSE RCM #:	2019-944
DMEPA Human Factors Evaluator:	Jason Flint, MBA, PMP
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

This memo conveys outstanding deficiencies related to human factors (HF) data for NDA 212045, naloxone HCl nasal spray. We provided HF advice on April 26, 2019 under IND 134954, indicating that the applicant would need to conduct another HF validation study to support their application^a (See Appendix B for additional background). However, the applicant did not submit new HF validation study results during this review cycle to support safe and effective use of the proposed product. Thus, we provide comments to the applicant for the Complete Response Letter in Section 2 below.

2 SUMMARY AND CONCLUSION

We conclude there is insufficient data to support the design of the user interface submitted in the marketing application. We provide the following letter ready comments for the Complete Response letter:

There is insufficient data or information to support the design of your proposed user interface. We refer you to our previous Human Factors Validation Study Advice Letter dated April 26, 2019 and Human Factors Validation Study Protocol Advice Letter dated August 9, 2019 under IND 134954. We request that you update your product's user interface, and use-related risk analysis, and submit the results of your HF validation study.

^a Chan, I. Human Factors Validation Study Protocol - Advice for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019APR26. RCM No.: 2019-367.

APPENDIX A. COMMUNICATIONS WITH INSYS, INC.^b

HF Validation Study Report Advice

https://darrrts.fda.gov//darrrts/faces/ViewDocument?documentId=090140af804f0292&_afRdirect=314453038601622

HF Validation Study Protocol Advice

https://darrrts.fda.gov//darrrts/faces/ViewDocument?documentId=090140af8050c34d&_afRdirect=314501492485010

APPENDIX B. BACKGROUND

Hikma Pharmaceuticals submitted a use-related risk analysis (URRA) and human factors (HF) validation study results report on April 30, 2019 under NDA 212045 for naloxone HCl nasal spray. We previously reviewed the same HF validation study results report under IND 134954 and provided recommendations in an advice letter dated April 26, 2019,^c including advice indicating that a new study would need to be conducted to support their marketing application, and we recommended they submit their HF validation study protocol for feedback before commencing a new study. Prior to us issuing the advice letter on April 26, 2019, a teleconference was held on April 8, 2019 with Hikma to convey preliminary concerns we identified with the results submitted. The sponsor was made aware that the Agency would soon be issuing an advice letter, and the applicant indicated their plan would be to address our recommendations once received^d. On June 13, 2019, the applicant submitted an HF validation study protocol. On August 9, 2019, we provided feedback on the applicant's HF validation study protocol^e.

^b On September 3, 2019 Insys submitted a notice of transfer of ownership in which they stated that all rights to the application were transferred to Hikma Pharmaceuticals USA Inc.

^c Chan, I. Human Factors Validation Study Protocol - Advice for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019APR26. RCM No.: 2019-367.

^d Mathew, D. Memorandum of Teleconference for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, PMS (US); 2019Apr17..

^e Chan, I. Human Factors Validation Study Protocol - Advice for Naloxone Nasal Spray IND 134954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019AUG09. RCM No.: 2019-367-1.

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, M.D., Pediatric Team Leader,
John J. Alexander, M.D., M.P.H., Deputy Director,
DPMH, ODE IV, OND

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

Drug: Naloxone Hydrochloride Nasal Spray

Applicant: Insys Development Company

Application Number: NDA 212045 (IND 134954)

Proposed Indication: Emergency treatment of known or suspected opioid
overdose, as manifested by respiratory and/or central
nervous system

Consult Request:
DAAP consulted DPMH to evaluate the applicant's pediatric assessment and provide
recommendations for pediatric use information in labeling.

Materials Reviewed:

- DPMH Consult Request (June 10, 2019) in DARRTS under NDA 212045
- Current Narcan (naloxone hydrochloride) nasal spray labeling, NDA 208411
(dated October 7, 2019 per FDALabel)

- Narcan (naloxone hydrochloride) injection labeling, NDA 016636 (dated February 11, 2002 per Drugs@FDA)
- Current Evzio (naloxone hydrochloride) autoinjector labeling, NDA 209862 (dated January 11, 2020 per FDALabel)
- Applicant's Proposed Labeling (dated August 6, 2019)
- Applicant's Agreed initial Pediatric Study Plan (iPSP) (dated November 29, 2018 in DARRTS under IND 134954 and submitted to NDA 212045 on April 30, 2019)
- Applicant's Pediatric Assessment, Nonclinical Overview and Human Factors Study (INS018-2-16) from the NDA 212045 submitted April 30, 2019
- Type C Meeting Minutes from February 22, 2018 for IND 134954 (dated March 14, 2018 in DARRTS)
- Written Response regarding the iPSP, IND 134954 (dated May 2, 2018 in DARRTS)
- Initial No Agreement Letter, IND 134954 (dated July 19, 2018)
- Pediatric Review Committee (PeRC) Meeting Minutes from meetings on March 14, 2018 and November 28, 2018, IND 134954 (dated April 20, 2018 and December 14, 2018, respectively)
- Advice Letter for juvenile toxicology protocol, IND 134954 (dated September 17, 2018)
- Prior DPMH consult reviews for Narcan (naloxone hydrochloride) nasal spray (NDA 208411) dated January 4, 2017 and November 10, 2015 and Evzio (naloxone hydrochloride) autoinjector (NDA 209862) dated September 23, 2016 in DARRTS

I. Background:

On April 30, 2019, Insys Development Company submitted a new drug application (NDA) seeking approval for naloxone hydrochloride nasal spray in all populations for emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system via the 505(b)(2) pathway with Narcan (naloxone hydrochloride) injection (NDA 016636) as the listed drug. Narcan injection is approved for the complete or partial reversal of opioid depression down to birth. The applicant proposes use for immediate administration as emergency therapy in settings where opioids may be present, including the community setting. This product proposes a higher dose of 8 mg compared to the 4 mg dose of the currently approved Narcan (naloxone hydrochloride) nasal spray (NDA 208411). Of note, Narcan 2 mg nasal spray (NDA 208411) and Narcan injection (NDA 016636) have been discontinued from marketing for reasons unrelated to safety. However, naloxone hydrochloride is approved and marketed as an injection under several abbreviated new drug applications and also as Evzio autoinjector 2 mg/0.4mL (NDA 209862). Table 1 describes the FDA approved naloxone products.

Table 1: FDA Approved naloxone products

Product	NDA number	Approved Pediatric Dose	Route of Administration	Marketing Status
Narcan (naloxone hydrochloride) nasal spray	208411	4 mg	IN	Marketed
		2 mg	IN	Discontinued
Narcan (naloxone hydrochloride) injection	016636	0.01-0.1 mg/kg (Adult dosing: 0.4-2 mg)	IV, IM, SQ	Discontinued
Naloxone hydrochloride injection	Multiple ANDAs	0.01-0.2 mg/kg (Adult dosing: 0.4-2 mg)	IV, IM, SQ	Marketed
Evzio autoinjector	209862	2 mg/0.4 mL	IM	Marketed

IN- intranasally, IV- intravenously, IM- intramuscularly, SQ- subcutaneously

Note all approved naloxone products are indicated for use down to birth for treatment of opioid overdose or depression.

II. DPMH Discussion of the Pediatric Assessment for NDA 212045

DAAP has previously publicly discussed and subsequently agreed upon a framework for approval of new naloxone products under development based upon demonstration of comparable or greater systemic exposures of naloxone during the early absorption phase as compared to an approved naloxone product given by an approved route of administration with literature data to support safety and dosing, in addition to necessary human factors studies, in adults and pediatric patients down to birth.¹ Of note, the applicant evaluated two formulations of their proposed product in the development program-- one containing 20% alcohol and the other containing (b) (4) % alcohol. However, the applicant is only seeking approval for the formulation containing 20% alcohol. Additionally, both formulations contain (b) (4) propylene glycol. The applicant submitted a pediatric assessment for pediatric patients from birth to less than 17 years of age which relies upon the following:

¹ FDA Briefing Document- Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee (October 5, 2016)

- (1) safety and effectiveness of other naloxone hydrochloride products administered intravenously (IV), intramuscularly (IM) and intranasally (IN) in the post-marketing setting that are approved for use in pediatric patients down to birth;
- (2) two comparative adult bioavailability studies—in one, a single dose of both Naloxone Nasal Spray 8 mg formulations containing 20% or (b)(4)% alcohol were compared with a single dose of 0.4 mg IM injection and in the other, a single dose of both Naloxone Nasal Spray 8 mg formulations containing 20% or (b)(4)% alcohol were compared with a single dose of 0.4 mg IM injection and 2 mg IV injection. The proposed naloxone product was compared to naloxone injection doses that are within the approved initial dose range (i.e., 0.4 to 2 mg) for the listed drug, Narcan injection. The Division determined that
 - a. a single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol (the final to-be-marketed formulation) exhibits comparable median T_{max} (15 min), greater unconjugated naloxone concentrations at all time points including earlier time points (i.e., 2, 4, 6, 8, 10 min post-dose), 14-fold greater C_{max} and 10-fold greater AUC_{last} or AUC_{0-inf} values than a single dose of 0.4 mg intramuscular (IM) injection. The relative bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol is 41.6 – 47.4% in comparison to an IM injection based on dose normalized exposure.
 - b. a single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol exhibits an unconjugated naloxone C_{max} value of 12.8 ng/mL, which is lower than the unconjugated naloxone concentration at 2 min post-dose (26.2 ng/mL) for a single dose of Narcan 2 mg IV injection. The absolute bioavailability is 36.6% for the Naloxone Nasal Spray 8 mg containing 20% alcohol in comparison to an IV injection based on dose normalized exposure.²
- (3) safety and dosing data for naloxone administered via IM, IV and IN routes available in the medical literature and clinical practice guidelines from organizations such as the American Academy of Pediatrics (AAP), European Medicines Agency (EMA) and the World Health Organization to support the proposed doses and administration.
- (4) a single IN dose juvenile animal toxicology study in rats to assess the safety of amounts of ethanol and propylene glycol contained in the proposed product for acute use in a pediatric population. In pre-NDA discussions³, DAAP noted concerns that exposure of immature animals to ethanol during the period of

² Clinical Pharmacology Review, NDA 212045 dated January 17, 2020 in DARRTS

³ Type C Meeting Minutes from February 22, 2018 for IND 134954 (dated March 14, 2018 in DARRTS)

- synaptogenesis (approximately 6 months gestation to several years after birth in humans) has been shown to trigger neuroapoptosis. Additionally, propylene glycol has also been associated with neuroapoptosis in addition to its other potential toxicity (seizures, agitation, cardiac arrhythmia, and acidosis). Therefore, the juvenile study needs to address potential effects of these excipients on these endpoints, particularly the central nervous system (CNS) effects. DAAP also advised the applicant to fully characterize the potential local and systemic toxicity of these components in pediatric patients.
- (5) A human factors study including adolescents 12 years of age and older in the user groups.

Literature Review

The applicant conducted a review of the published literature that identified the following data to support safety of the proposed naloxone dose in the full pediatric population:

- Sixteen published case reports between 1973-2018⁴ of pediatric patients administered intravenous (IV) naloxone to reverse drug overdose effects describe patients 25 days to 16 years of age who received doses of 1 mg to 48.84 mg corresponding to 0.1 to 2.72 mg/kg over a duration of a single dose to 65.5 hours without adverse events. Patients administered a single IV dose ranged in age from 11 months to 4.5 years at doses of 1.6 to 20.6 mg.
- Two case reports of neonates with serious adverse events attributed to naloxone from acute opioid withdrawal
 - A newborn born to a heroin abuser with antenatal methadone exposure at the onset of labor had respiratory distress for which she was treated with naloxone 0.2 mg IM. She developed generalized convulsions 2 minutes later which failed to respond to diazepam, paraldehyde and a loading dose of phenobarbitone, and were ultimately terminated with a bolus of morphine followed by a continuous morphine infusion that was tapered and discontinued after a week.⁵
 - A 27 week-old infant being ventilated for respiratory distress syndrome, was given tenfold morphine overdose (bolus of 100 mcg/kg) on day 7 for sedation resulting in a fall of her arterial blood pressure. She was given naloxone IV (dose of 100 mcg/kg or 0.049

⁴ See Table 1 from Applicant's Pediatric Assessment, NDA 212045, submitted April 30, 2019

⁵ J Gibbs, T Newson, J Williams, DC Davidson. Naloxone Hazard in Infant of Opioid Abuser. The Lancet, 1989 Jul 15: 159-160.

mg) and immediately developed bradycardia and asystole. She was responded to cardiopulmonary resuscitation and a bolus of adrenaline.⁶

Reviewer comment: Proposed labeling includes a subsection in the Warning and Precautions section on Precipitation of Severe Opioid Withdrawal consistent with other naloxone product labeling which describes risks of withdrawal to persons including newborns of mothers who are known or suspected to be physically dependent on opioids precipitated by naloxone use.

- Three case reports^{7,8,9} of pulmonary edema in four adolescents (13-17 years of age) after 0.08 to 0.5 mg doses (0.0012 to 0.0037 mg/kg)

Reviewer comment: Proposed labeling includes a subsection in the Warning and Precautions section on Risk of Cardiovascular Effects consistent with other naloxone product labeling which describes the risk of pulmonary edema with abrupt postoperative reversal of opioid depression after using naloxone hydrochloride.

- Retrospective chart review¹⁰ of 195 pediatric patients (0-18 years of age) examining cardiorespiratory changes and complications following naloxone treatment
 - Group 1: postoperative children who underwent fentanyl-supplemented general anesthesia for various surgical procedures (n=116, mean $\pm$ standard deviation (SD) age 10.6 $\pm$ 5.3 years)
 - Group 2: children presenting to the emergency department or admitted to the pediatric intensive care unit for altered sensorium or respiratory depression (n=79, mean age 8.2 $\pm$ 6.7 years).
 - None of the patients in the study developed arrhythmias, hypotension, seizures, emesis, or cardiac arrest after naloxone administration at total doses ranging from 0.01 to 7 mg (0.001 to 0.5 mg/kg body weight) with a median dose of 0.1 mg.
 - One patient developed progressive hypoxia and bradycardia requiring tracheal intubation within five minutes of 2 mg IV naloxone administration by emergency medical services; acute pulmonary edema was subsequently confirmed.

⁶ G Deshpande, A Gill. Cardiac arrest following naloxone in an extremely preterm neonate. Eur J Pediatr (2009) 168:115–117.

⁷ Prough DS, Roy R, Bumgarner J, Shannon G. Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. Anesthesiology. 1984 May;60(5):485-6.

⁸ Harrington LW. Acute pulmonary edema following use of naloxone: a case study. Crit Care Nurse. 1988 Dec;8(8):69-73

⁹ C Johnson, P Mayer D Grosz. Pulmonary Edema Following Naloxone Administration in a Healthy Orthopedic Patient J. Clin. Anesth., vol. 7, June 1995

¹⁰ RA Hasan, AS Benko, BM Nolan, J Campe, J Duff, and GY Zureikat. Cardiorespiratory Effects of Naloxone in Children. Ann Pharmacother. 2003 Nov;37(11):1587-92.

Reviewer comment: The literature review describing IV and IM use of naloxone in the full pediatric population at doses far exceeding those approved for naloxone injection did not identify new safety signals that are not already included as adverse reactions in the labeling of FDA-approved naloxone products. Given the lower bioavailability of the of to be marketed IN product compared to naloxone 0.4 IM and naloxone 2 mg IV, this literature data supports safe use at the proposed doses for this product.

Safety of the Propylene Glycol and Ethanol levels

Propylene Glycol in Children:

The (b) (4)% and 20% alcohol formulations both contain (b) (4) propylene glycol which is equivalent to (b) (4) of propylene glycol per actuation, respectively. The European Medicines Agency's guidelines for maximum recommended daily doses of propylene glycol in the pediatric population¹¹, irrespective of duration or route of administration, are outlined in Table 2 below. Based on these recommendations and the one-time intended use of the product, the applicant contends that the proposed amount of propylene glycol should not pose a safety risk in patients down to birth.

Reviewer comment: While the proposed product is designed for single use, labeling recommends repeat dosing every 2-3 minutes as needed. Nevertheless, even for the most stringent of these recommended limits (i.e., 1 mg/kg for neonates), the amount of propylene glycol would not be exceeded even if up to seven doses were administered.

¹¹ European Medicines Agency's Background review for propylene glycol

(b) (4)

Source: Applicant's Agreed iPSP, IND 134954, submitted to NDA 212045

Ethanol in Children:

The (b) (4)% and 20% alcohol formulations contain (b) (4) alcohol per spray, respectively and deliver (b) (4) µL (one dose) to (b) (4) µL (four doses) and (b) (4) µL (one dose) to (b) (4) µL (four doses), respectively. The American Academy of Pediatrics' Committee on Drugs has established a blood alcohol concentration (BAC) limit of 25 mg/100 mL following a single dose of alcohol-containing medication. The ethanol single dose limits proposed by the American Academy of Pediatrics (AAP)¹² ranged from 2.3 to 7.3 mL for ages 2 and 12 years at average weight for age, respectively. Therefore, based on these recommendations, the applicant contends that the quantity of ethanol delivered per treatment is well below the recommended limits. Additionally, the applicant asserts that the amount of alcohol administered with the proposed product is nominal and below the maximum allowed dose limit for pediatric over-the-counter products; moreover, the treatment is a one-time event.

Reviewer comment: Although the proposed amounts of ethanol fall within these AAP guideline ranges described for patients 2 to 12 years of age, this threshold was arbitrarily selected based on CNS effects being identified at BAC 100 mg/100 mL (0.1%)

¹² PEDIATRICS Vol. 73 No. 3 March 1984

and data on ethanol metabolism and toxicity in pediatric patients are limited.¹³ Moreover, a safe level of ethanol exposure in neonates and infants has not been established.¹⁴ Furthermore, as noted above, DAAP has expressed concerns regarding neuroapoptosis and other CNS effects in addition to local and systemic toxicity with ethanol and propylene glycol exposure in neonates and infants. Therefore, DAAP advised the applicant to conduct a juvenile animal study to assess the potential effects of these excipients to support safe use in patients down to birth. The applicant negotiated the design of the study with DAAP.

Considerations in Nasal Absorption

The applicant considered whether differences in nasal absorption between adult and pediatric patients would impact efficacy or safety. The applicant noted that differences in absorption of drugs through the nasal mucosa are expected in pediatric patients, including neonates, compared to adults based on the following factors:

- differences in nasal volume and nasal morphology with variability in the pattern of deposition of intranasally administered particles in patients less than 5 years of age compared to older pediatric patients and adults^{15, 16}
- physicochemical properties of the drug^{17, 18}
- mucociliary clearance and medical conditions such as rhinitis or polyps^{19, 20}
- variability of shape and magnitude of the nasal cavity^{16, 17, 21}

Nevertheless, based on the review of published literature which showed that pediatric patients, who received well over the proposed 8 mg naloxone as a single dose by IV route of administration, had no adverse effects and thus a wide margin of safety. The applicant contended that the proposed 8 mg dose for the nasal spray in the pediatric population is anticipated to have a tolerable safety profile.

¹³ DPMH review for amlodipine oral solution, PIND (b) (4), dated December 11, 2019 in DARRTS

¹⁴ Marek E, Kraft WK. Ethanol Pharmacokinetics in Neonates and Infants. *Current Therapeutic Research*. 2014;76:90-97.

¹⁵ M Baczek, E Hassmann-Poznanska. Nasal airway dimensions in children, measured by acoustic rhinometry. *New Medicine*. 1999 Mar.

¹⁶ Xi J, Si X, Zhou Y, Kim J, Berlinski A. Growth of nasal and laryngeal airways in children: implications in breathing and inhaled aerosol dynamics. *Respir Care*. 2014 Feb;59(2):263-73.

¹⁷ Grassin-Delyle S, Buenestado A, Naline E, Faisy C, Blouquit-Laye S, Couderc LJ, Le Guen M, Fischler M, Devillier P. Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids. *Pharmacol Ther*. 2012 Jun;134(3):366-79.

¹⁸ HR. Costantino, L Illum, G Brandt, PH. Johnson, SC Quay. Intranasal delivery: Physicochemical and therapeutic aspects. *International Journal of Pharmaceutics* 337 (2007) 1–24.

¹⁹ L Illum. Nasal drug delivery—possibilities, problems and solutions. *Journal of Controlled Release* 87 (2003) 187–198.

²⁰ E Martin, NGM Schipper, JC Verhoef, FWHM Merkus. Nasal mucociliary clearance as a factor in nasal drug delivery. *Advanced Drug Delivery Reviews* 29 (1998) 13–38.

²¹ N Mygind, R Dahl. Anatomy, physiology and function of the nasal cavities in health and disease. *Advanced Drug Delivery Reviews* 29 (1998) 3–12.

Reviewer comment: Labeling for other naloxone products and proposed labeling for this product describe the erratic or delayed absorption of naloxone in pediatric patients. However, despite likely differences in absorption from adults, administration of the proposed dose appears safe based on the wide safety margin of naloxone identified in the literature review.

Safety of Proposed Administration Volume

The proposed administration volume for the product is 100 µL per actuation. This volume is identical to the volume per actuation of Narcan nasal spray which is approved down to birth. Furthermore, the applicant acknowledged the smaller nasal volume of infants but noted that the dose delivered would still be expected to be effective even if the full 8 mg dose is not absorbed.

Reviewer comment: The proposed volume does not exceed previously approved doses and given that intranasal doses down to 2 mg have been found to safe and effective by the FDA (i.e., Narcan 2 mg nasal spray), the applicant's contention that even if the full 8 mg dose is not absorbed, delivered dose is likely to be effective seems reasonable.

Adequacy of the Nasal Actuator

The proposed delivery device is identical in size to the approved and marketed Narcan nasal spray device, and the applicant contends that the nasal actuator for the proposed product will adequately administer the product to patients down to birth. Furthermore, the applicant asserts that although the nasal tip may not be inserted completely inside of the nares of all pediatric patients the way it can be done for adults, as infants have nares of about 3 mm in diameter, the opening at the tip of the device through which the medication is administered is small enough (b) (4) in diameter) to deliver the medication into the nose of any human subject, if properly positioned.

Reviewer comment: The FDA has previously evaluated the same intranasal delivery device for pediatric use during the approval of Narcan Nasal Spray and determined that it is adequate for administration in patients down to birth.²²

²² DPMH consult review for Narcan nasal spray, NDA 208411, dated January 4, 2017

Juvenile Toxicity Study

In accordance with DAAP guidance,²³ the applicant conducted a juvenile animal study in rats with a human equivalent age of a preterm neonate to identify a no-observed-adverse-event level of naloxone and excipients and to fully characterize the potential local and systemic toxicity of these components in pediatric patients, particularly with respect to ethanol and propylene exposure and the effects on the CNS. The juvenile rat study dosed rat pups with 0, 1.6, 2.4, or 3.2 mg/day naloxone using both formulations containing 20% or (b) (4) % alcohol in combination with (b) (4) propylene glycol as well as a saline control intranasally in divided doses, one per nostril as a single daily dose with a 28-day recovery period. All groups were examined for neurohistopathology, sexual maturity, social behavior, and learning and memory at appropriate timepoints and there were no effects from intranasal administration of naloxone or excipients on any of these endpoints.

Reviewer comment: The juvenile animal study appears to have been well conducted in accordance with DAAP guidance and supports the safe use of the proposed product in the pediatric population down to birth. Furthermore, the study is reassuring to address the knowledge gaps regarding safe level of ethanol exposure in neonates and infants with single dose administration.

Human Factors Study

The applicant conducted a human factors study including 31 lay user adults ages 20 to 70 years with normal literacy levels, youth ages 12 to 17 years, and adults with low-literacy levels using a mannequin to simulate an overdosed unconscious individual.

Reviewer comment: The mannequin used in the study appears to be adult-sized. Human factors studies including mannequins that resemble infants and neonates and caregivers of younger children would more fully assess proper dosing delivery to the proposed population.

IV. DPMH Conclusions on the Pediatric Assessment

The PK assessment and literature data adequately demonstrate the safety and effectiveness of the proposed dose of naloxone for all pediatric age ranges, including neonates. Additionally, the proposed device and administration volume is identical to that approved for Narcan Nasal Spray, which also supports the safe and effective

²³ Advice Letter for juvenile toxicology protocol, IND 134954 (dated September 17, 2018)

administration of the proposed product to pediatric patients, including neonates. Given the one-time use in an emergency setting with negative findings on the juvenile animal studies and acceptable safety profile, the risk benefit of this product for pediatric patients down to birth is favorable.

DAAP presented the pediatric assessment to the PeRC on January 28, 2019. The PeRC recommended that the Division request the applicant conduct human factor studies that assess use in infants and include caregivers of infants; however, if these studies were not previously requested it may be difficult to request them now. Therefore, the Division will discuss the review of the human factors study and future study plan design with the Division of Medication Error Prevention and Analysis. The Division should also consider these recommendations in the design of human factors studies for future naloxone product development as well.

V. DPMH Review of Pediatric Use Labeling:

The applicant plans to rely on the currently approved labeling for Narcan Injection (NDA 016636) and published literature to support the pediatric labeling. Labeling from approved naloxone hydrochloride products was taken into consideration in the review and development of our labeling recommendations. This DPMH labeling review will focus on edits to Section 1 (Indications and Usage), Section 5 (Warnings and Precautions), and Subsection 8.4 (Pediatric Use). The following recommendations are based on labeling discussions between DAAP and DPMH. Underlined text represents proposed additions and strikethroughs in the relevant text represent proposed deletions.

Application Holder's Proposed Labeling:

1 INDICATIONS AND USAGE

TRADENAME (b) (4) is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients.

TRADENAME (b) (4) is intended for immediate administration as emergency therapy in settings where opioids may be present.

TRADENAME (b) (4) is not a substitute for emergency medical care.

Reviewer Comment: The Guidance for Industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and

Format²⁴ states The INDICATIONS AND USAGE section should clearly communicate the scope of the approved indication, including the population to which the determination of safety and effectiveness is applicable. Additionally, the March 2019 Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling states that if the product is indicated in the entire pediatric population, the term pediatric patients or pediatric population should be incorporated into the indication statement. For example: “DRUG X is indicated for the treatment of Indication Y in adult and pediatric patients.”

5 WARNINGS AND PRECAUTIONS

5.3 Precipitation of Severe Opioid Withdrawal

(b) (4)



²⁴ Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format: Guidance for Industry (Draft Guidance). July 2018.
<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm612697.pdf>

(b) (4)

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

Reviewer comment: Relevant non-proprietary language in other naloxone hydrochloride products should be included in this labeling for consistency among labeling in this class.

8.4 Pediatric Use

(b) (4)

Absorption of naloxone hydrochloride following intranasal administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds appropriately to naloxone hydrochloride, he/she must be carefully monitored for

at least 24 hours, as a relapse may occur as naloxone hydrochloride is metabolized.

In opioid-dependent pediatric patients, (including neonates), administration of naloxone hydrochloride may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it may be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone hydrochloride product that can be dosed according to weight and titrated to effect. [see Warnings and Precautions (5.3)].

(b) (4)

Reviewer comment: The March 2019 Pediatric Labeling Guidance states that this section should describe the basis for approval. This approval relied on FDA's determination of safety and effectiveness for the listed drug, Narcan injection, the labeling for which does not describe the clinical studies supporting approval for this reviewer to determine if the pivotal studies were adequate and well-controlled. This approval relied upon two pivotal relative bioavailability studies in healthy adults in addition to dosing and safety data from other naloxone hydrochloride products. Additionally, relevant non-proprietary language in other naloxone hydrochloride products should be included in this labeling for consistency among labeling in this class. The proposed language (b) (4)

(b) (4) is not included in other naloxone product labeling and should be justified by the applicant to determine if that language is appropriate to include in the labeling for this particular naloxone product. Although, in general, juvenile animal data should not be included in labeling when the data do not suggest an adverse signal, a safe level of ethanol exposure has not been determined for neonates and ethanol and propylene glycol have been associated with CNS effects such as neuroapoptosis in addition to other systemic toxicities. Therefore, describing the negative findings from the juvenile animal study in labeling would provide useful safety information regarding the exposure to ethanol and propylene glycol in this population to prescribers. Furthermore, labeling this information would publicly document the findings from this study and inform the development programs for future naloxone products

thereby obviating the need to unnecessarily sacrifice animals in a repeat study. Pharmacology Toxicology reviewers will propose language describing the relevant results of the study.

VI. DPMH Actions and Labeling Recommendations:

DPMH reviewed the applicant's draft labeling. DPMH provided recommended labeling for the pediatric population based on labeling discussions between DAAP and DPMH and in accordance with 21 CFR 201.57(c)(9)(iv). DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the application holder and may not fully reflect changes suggested here.

Note that the Division plans to issue a Complete Response to this application due in large part to manufacturing issues and minor non-clinical deficiencies which do not impact the clinical assessment.

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

PATIENT LABELING REVIEW

Date: January 31, 2020

To: Sandy Truong, PharmD
**Division of Anesthesiology, Addiction, and Pain
Medicine (DAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Nima Ossareh, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review Deferred: Patient Package Insert (PPI) and
Instructions for Use (IFU)

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

Dosage Form and Route: nasal spray

Application Type/Number: NDA 212045

Applicant: Insys Therapeutics, Inc.

1 INTRODUCTION

On April 30, 2019, Insys Therapeutics, Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 212045 for TRADENAME (naloxone hydrochloride) nasal spray. This application references the currently approved product NARCAN (naloxone hydrochloride) injection (NDA 016636). The proposed indication for this application is for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

On June 7, 2019, the Division of Anesthesiology, Addiction, and Pain Medicine (DAAP) requested that the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (naloxone hydrochloride) nasal spray.

This memorandum documents the DMPP and OPDP review deferral of the Applicant's proposed PPI and IFU for TRADENAME (naloxone hydrochloride) nasal spray.

2 CONCLUSIONS

Due to outstanding deficiencies, DAAP plans to issue a Complete Response (CR) letter. Therefore, DMPP and OPDP defer comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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

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

Date of This Review:	December 5, 2019
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	DA 21204
Product Name and Strength:	(naloxone hydrochloride) nasal spray, 8 mg/0.1 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	HIKMA PHARMACEUTICALS USA INC
FDA Received Date:	August 6, 2019
OSE RCM #:	2019-943
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for naloxone hydrochloride nasal spray, DAAP requested that we review the proposed container label, carton labeling, Instructions for Use (IFU) and Prescribing Information (PI) for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

This naloxone hydrochloride nasal spray product, NDA 212045, was submitted as a 505(b)(2) NDA and the listed drug product is naloxone hydrochloride injection NDA 016636. We note that when NDA 212045 was originally submitted on April 30, 2019, the Applicant was Insys Development Company (Insys). During our initial review of the application, Insys submitted a human factors (HF) validation study protocol under their IND 134954. We reviewed the protocol, instructions for use, container labels and carton labeling and provided recommendations to Insys on August 7, 2019.^a On September 3, 2019 Insys submitted a notice of transfer of ownership in which they stated that all rights to the application were transferred to Hikma Pharmaceuticals USA Inc (Hikma). We contacted Hikma to inquire when they planned to submit the results of the HF validation study. Hikma replied that they would submit the results at the end of March 2020.

Results from the pending HF validation study may impact our labeling recommendations for the container label, carton labeling, and IFU. However, DAAP would like our recommendations for the PI. Therefore, we will reserve our review of the container label, carton labeling, and IFU, when Hikma submits the results of their HF validation study. We provide our recommendations for the PI only in this review to facilitate discussions during forthcoming labeling meetings.

3 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

^a Flint, J. Human Factors Validation Study Protocol Review for Naloxone Nasal Spray. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 07. RCM No.: 2019-367.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

*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

4 FINDING, RECOMMENDATION, AND CONCLUSION

Our evaluation of the proposed naloxone hydrochloride PI identified an area of vulnerability that may lead to medication errors. Table 2 below includes the identified medication error issue with the submitted PI, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

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 16 How Supplied/Storage and Handling			
1.	The How Supplied/Storage and Handling section does not include the National Drug Code (NDC) for the carton labeling.	Per 21 CFR 201.57(c)(17), this section should include appropriate information to facilitate identification of the dosage form, including the assigned NDC.	The carton labeling includes the NDC as, (b) (4). Add this NDC to the How Supplied/Storage and Handling section.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for naloxone hydrochloride that HIKMA PHARMACEUTICALS USA INC submitted on August 6, 2019, and the listed drug (LD).

Table 3. Relevant Product Information for Listed Drug and naloxone hydrochloride		
Product Name	Naloxone hydrochloride	naloxone hydrochloride
Initial Approval Date	April 13, 1971	N/A
Active Ingredient	Naloxone HCl	Naloxone HCl
Indication	Opioid overdose	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	8 mg/0.1 mL
Dose and Frequency	dependent on indication and patient specific variables	Administer a single spray (8 mg) of TRADENAME Nasal Spray to adults or pediatric patients intranasally into one nostril. Administer additional doses of TRADENAME Nasal Spray, using a new nasal spray with each dose, if the patient does not respond or responds and then relapses into respiratory depression, additional doses of TRADENAME Nasal Spray may be given every 2 to 3 minutes until emergency medical assistance arrives
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	Room temperature	Room Temperature
Container Closure	Multiple dose vials, ampules, (b) (4)	(b) (4) Intranasal Device

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 4, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, naloxone or NDA 212045 or IND 134954. Our search identified two previous reviews^{b,c}, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. – N/A

APPENDIX D. – N/A

APPENDIX E. – N/A

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,^d along with postmarket medication error data, we reviewed the following naloxone hydrochloride labels and labeling submitted by HIKMA PHARMACEUTICALS USA INC on August 6, 2019.

- Prescribing Information (Image not shown) but can be accessed in EDR via:
 - o <\\cdsesub1\evsprod\nda212045\0008\m1\us\draft-label-tc.docx>

^b Flint, J. Human Factors Study Report and Labels and Labeling Review for Naloxone Nasal Spray. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 26. RCM No.: 2019-367.

^c Flint, J. Human Factors Validation Study Protocol Review for Naloxone Nasal Spray. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 07. RCM No.: 2019-367

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

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