CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212045Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA # 212045
Assessment # 2

Drug Product Name	Naloxone Nasal Spray
Dosage Form	Nasal Spray
Strength	8 mg
Route of Administration	intranasal
Rx/OTC Dispensed	Rx
Applicant	Hikma Pharmaceuticals USA Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 24; eCTD 0023	29 Oct 20	All
Supporting document 29; eCTD 0028	11 Feb 21	Drug product
Supporting document 31; eCTD 0030	5 Mar 21	Drug product
Supporting document 32; eCTD 0031	15 Mar 21	Drug product
Supporting document 34; eCTD 0033	19 Mar 21	Drug product
Supporting document 35; eCTD 0034	24 Mar 21	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sam Bain	Donna Christner
Drug Product	Jizhou Wang	Julia Pinto
Manufacturing	Yeung Chan	Yaodong (Tony) Huang
Microbiology	Julia Marre	Neal Sweeney
Biopharmaceutics	N/A	N/A
CDRH – facility consult	Michaela Schulman	Rumi Young

Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Jizhou Wang	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The CMC recommendation for this resubmission is approval.
Drug product recommends approval with post-marketing commitments.
Process/manufacturing recommend approve in this review cycle.
Drug substance and microbiology recommended approval in the previous review cycle and their recommendation remains approve.

The proposed shelf-life of 24 months is acceptable when stored at 20-25°C (68-77°F) with excursions permitted to 40°C (104°F) and to 5°C (41°F). (b) (4)

See also CMC IQA review 1 dated 30 Jan 2020.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This resubmission is a response to a complete response letter dated 28 Feb 20.

Naloxone Nasal Spray is a clear, colorless to yellow solution and is filled into clear glass vials, stoppered, and fitted with a unit-dose nasal spray device. The unit-dose spray device delivers about 100 microliters of Naloxone Nasal Spray, in turn delivering 8 mg of naloxone hydrochloride per spray.

The proposed shelf-life of 24 months is acceptable when stored at 20-25°C (68-77°F) with excursions permitted to 40°C (104°F) and to 5°C (41°F). (b) (4)

Proposed Indication(s) including Intended Patient Population	1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. 2. Immediate administration as emergency therapy in settings where opioids may be present.

Duration of Treatment	acute
Maximum Daily Dose	16 mg (as proposed by the applicant)
Alternative Methods of Administration	Injection, intramuscular and intravenous with dose adjustment

B. Quality Assessment Overview

Drug Substance: Adequate

We have looked at the referenced DMF (b) (4) for any possible change in the drug substance CMC. The CMC changes in the DMF since the NDA Complete Response letter do not change the quality of the drug substance, and the DMF is presently adequate.
The DMF holder currently has a retest period of (b) (4) for the drug substance with a shelf-life storage condition of (b) (4)
The drug substance CMC remains adequate; and the NDA remains recommended for approval from the drug substance perspective.

See also CMC IQA review 1 dated 30 Jan 2020.

Drug Product: Adequate

In this resubmission, the sponsor has adequately tightened the cceptance criteria for specified impurity, assay of edetate disodium dihydrate (EDTA), total impurities, pH, spray pattern, droplet size distribution, spray content uniformity based on stability data trends.

The sponsor revealed that the non-reproducibility of the original method is the root cause for the significant fluctuation for the assay of EDTA on stability. A new analytical method has been developed and validated to achieve acceptable reproducible results.

Guided by a more conservative AET, the sponsor has performed a new extractables studies to address the issues of inappropriate sample preparation and narrow pH range (b) (4) in the original submission by expanding the pH range (b) (4) and (b) (4)

To address the issues on lack of leachables method validation in the original submission, the sponsor has fully validated the leachables methods for representative volatile, semi-volatile and non-volatile compounds. The sponsor has also adequately developed and validated leachables methods for special-case compounds including (b) (4) (b) (4) (b) (4) that may be present in the rubber stoppers.

Per Agency's recommendation, the sponsor has performed accelerated (40°C/75% RH) and long-term (25°C/60% RH and 5°C ± 3°C) for 3 new registration batches with inverted and upright orientation. Data of up to 9 month under accelerated and long studies against revised specifications fall into the revised specification.

Based on the 6 months of accelerated and 24 months of real-time stability data, a 24 months of shelf life proposed in the original submission is justified when stored at 20-25°C (68-77°F) with excursions permitted from 4°C to 40°C (39°F to 104°F). Since the out of specifications (OOSs) happened for unspecified impurities and pH at accelerated storage conditions (40°C/75%RH) for at least 3 batches at optional 18 and/or 24 month time points, a note that "Avoid long storage at temperature higher than 40˚C" should be include in the label.

In conclusion, we recommend the drug product to be approved with Post Marketing Commitments (PMC) as outlined below.

1.To address the Agency's concerns about aqueous extractions by using Autoclave at ~121˚C for 1 hour, Hikma committed to accomplishing the following additional extractables study and report the results to the Agency upon completion of the laboratory work and data analysis (03/15/2021 Response):

a.An additional extraction study on 1 lot of (b) (4) Stoppers using pH 2.5 and pH 9.5 aqueous extracting solutions, using an autoclave (eight 90 min cycles, with samples analyzed at 3 hours, 6 hours, 9 hours and 12 hours). Analysis for semi-volatile and non-volatile extractables will be accomplished on samples from each time-point.

b.An additional extraction study on 1 lot (same lot as in the above autoclave study) of (b) (4) Stoppers using pH 2.5 and pH 9.5 aqueous extracting solutions with reflux for 24 hours. At the end of the 24-hour period, samples from each aqueous extract will be analyzed for semi-volatile and non-volatile extractables.

2.To address the Agency's concerns about the limited structural characterization of the extractables in the resubmission, Hikma committed to accomplishing the following studies and report the results to the Agency upon completion of laboratory work and data analysis (03/15/2021 Response):

a.A systematic reanalysis of the original Chemic extractables assessments with the goal of at least assigning a compound class to each unknown extractable discovered. Compound class identification would take an individual identification level from "Unknown" to "Tentative".

b.Additional extraction studies with supplementary data acquisition (e.g., high-resolution accurate mass measured LC/MS and tandem mass spectrometry, LC/MS/MS) to support identification efforts for extractables.

3.To address the Agency's concerns about incomplete leachables method validation, Hikma committed to accomplishing the following leachables method validation study and report the results to the Agency upon completion of the laboratory work and data analysis (03/15/2021 Response):

a.Additional experiments (including Accuracy) to extend the validations for volatile, semi-volatile and non-volatile leachables to additional potential leachables (i.e., extractables) based on the additional consideration and extension of extractables identifications.

b.Additional experiments with (b) (4) drug product at appropriate levels relative to the AET to confirm that these extractables would be discovered by the leachables analytical methods (e.g., volatile, semi-volatile and non-volatile leachables).

4.Hikma committed to performing a drug product spiking study using the following requested compounds to demonstrate that the validated leachables methods can detect these potential leachables at AET level with satisfactory S/N (03/19/2021 Response):

(b) (4)

(b) (4) (observed in current extractable study)

7.Hikma committed to monitoring the leachables at RRT (b) (4) throughout the leachables stability study (03/24/2021 Response).

8.Hikma committed to investigating the data discrepancies between the current leachables studies submitted on 03/15/2021 and the previous studies. Specifically, (b) (4) (03/24/2021 Response).

9 Hikma committed to (b) (4)

(b) (4)

(b) (4) demonstrate that the validated leachables methods can detect these potential leachables at AET level with satisfactory S/N (03/24/2021 Response).

See also CMC IQA review 1 dated 30 Jan 2020.

Labeling: Adequate

Manufacturing: Adequate

The drug product manufacturing process operations include [redacted]. No scale up has been proposed. First cycle review deficiencies associated with [redacted] extractable and leachable risks [redacted] are sufficiently addressed.

The drug substance manufacturing facility has experience manufacturing the API and is currently cGMP compliant and is deemed approvable at this time. The drug product facility has experience manufacturing nasal sprays and has successfully completed site transfer and qualification of entire manufacturing line and is currently cGMP compliant and also deemed approvable at this time.

See also CMC IQA review 1 dated 30 Jan 2020.

Biopharmaceutics: Choose an item.

N/A

Microbiology (if applicable): Adequate

No significant changes were made in this response to the 28 February 2020 Complete Response Letter (CRL) that affect the sterility assurance of the drug product.
See also CMC IQA review 1 dated 30 Jan 2020.

QUALITY ASSESSMENT DATA SHEET

See CMC IQA review 1 dated 30 Jan 2020.

44 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Not provided	Inadequate
Established name(s)	naloxone hydrochloride Nasal Spray	Adequate
Route(s) of administration	nasal spray	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Nasal Spray: 8 mg of naloxone hydrochloride in 0.1 mL	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose	Adequate

1.2 FULL PRESCRIBING INFORMATION

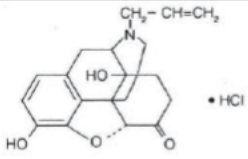
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	No	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Nasal spray	Adequate
Strength(s) in metric system	a single 8 mg dose of naloxone hydrochloride in 0.1 mL intranasal spray.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Clear, colorless to yellow solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	naloxone hydrochloride	Adequate
Dosage form(s) and route(s) of administration	nasal spray	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	dehydrated alcohol (20% (w/w)) edetate disodium dihydrate, propylene glycol, purified water, and sodium hydroxide/hydrochloric acid to adjust pH	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Dehydrated alcohol (20% (w/w)	
Statement of being sterile (if applicable)	N/A	
Pharmacological/therapeutic class	an opioid antagonist	
Chemical name, structural formula, molecular weight	 Chemical name: 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride Molecular formula: C19H21NO4•HCl Molecular weight: 363.84 g/mol	
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	The pH range is (b) (4). (should be 4.0 to 5.5)	Inadequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	(b) (4)	Adequate
Strength(s) in metric system		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single use	Adequate

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	.No	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and	N/A	Adequate

desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store TRADENAME Nasal Spray in the blister and cartons provided. Store at 20-25ºC (68ºF to 77ºF), excursions permitted to 40°C (104°F) and to 5°C (41°F)	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Not provided	Inadequate
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4)	Adequate

2.0 PATIENT LABELING

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

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	TRADENAMETM (Naloxone HCl)	Acceptable
Dosage strength	8 mg	Acceptable
Route of administration	nasal spray	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	Acceptable
Net contents (e.g. tablet count)	Yes	Acceptable
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	Yes	Acceptable
Lot number and expiration date	Yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Yes 20% w/w	Acceptable
Bar code		Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	yes	Acceptable
Medication Guide (if applicable)	yes	Acceptable
No text on Ferrule and Cap overseal	N/A	Acceptable
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	Acceptable
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: ***Inadequate***

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

ITEMS FOR ADDITIONAL ASSESSMENT

a.

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date:
Secondary Assessor Name and Date (and Secondary Summary, as neede

APPEARS THIS WAY ON ORIGINAL

Jizhou Wang

Digitally signed by Jizhou Wang
Date: 3/29/2021 12:56:00PM
GUID: 53160853000083c4052c25f3a3cf964a

Julia Pinto

Digitally signed by Julia Pinto
Date: 3/29/2021 01:16:13PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 212045
Drug Product Name	Naloxone Nasal Spray
Strengths	8 mg
Dosage Form	Spray
Administration Route	Nasal
Indication	1) Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. 2) Immediate administration as emergency therapy in settings where opioids may be present.
Applicant Name	Hikma Pharmaceuticals USA Inc.

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

The drug product manufacturing process [redacted] No scale up has been proposed. First cycle review deficiencies associated with [redacted], and extractable and leachable risks [redacted] are sufficiently addressed.

The drug substance manufacturing facility has experience manufacturing the API and is currently cGMP compliant and is deemed approvable at this time. The drug product facility has experience manufacturing nasal sprays and has successfully completed site transfer and qualification of entire manufacturing line and is currently cGMP compliant and also deemed approvable at this time.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original NDA (0000)	04/30/2019
Amendment – 8 (0007)	07/17/2019
Amendment – 9 (0008)	08/06/2019
Amendment – 11 (0010)	09/03/2019
Amendment – 12 (0011)	09/04/2019
Amendment – 15 (0014)	09/10/2019
Amendment – 16 (0015)	09/20/2019

Amendment – 17 (0016)	10/18/2019
CR Resubmission – 24 (0023)	10/29/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

- [redacted] (b) (4)
- No leachable and extractable studies
- IPC specifications for pH, viscosity, and density requested
- [redacted] (b) (4)

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

1. *Post-Approval Commitments and Lifecycle Management Considerations*

Postmarketing commitments (PMC)?	No
Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. *Facilities Table*

Facility name and address	FEI	Responsibilities and profile code(s)	Status
West-Ward Columbus Inc. 1809 Wilson Road, Columbus, Ohio, USA, 43228	1510690	[redacted] (b) (4) drug product manufacturing, packaging, and labeling; drug product release and stability testing; drug product microbiological testing || 356h Status: Active LIQ MSO	Approve - Based on Previous History
[redacted] (b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			No Evaluation Necessary

20 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Yeung Chan

Digitally signed by Yeung Chan
Date: 2/24/2021 08:59:57AM
GUID: 589b227e0043a984b5ef04213b12b53e

Yaodong Huang

Digitally signed by Yaodong Huang
Date: 2/24/2021 09:31:27AM
GUID: 5314c51b00004fc086ceeaa91af8e9da

CHAPTER VII: MICROBIOLOGY

Product Information	This is a non-sterile, aqueous, single-use, nasal spray drug product that is indicated in the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. This drug product is packaged in a unit-dose spray device that delivers the entire contents of the drug product in one spray (single-use).
NDA Number	212-045
Assessment Cycle Number	002
Drug Product Name/ Strength	Naloxone Nasal Spray (Naloxone Hydrochloride, USP), 8 mg
Route of Administration	Nasal spray
Applicant Name	Hikma Pharmaceuticals USA Inc.
Therapeutic Classification/ OND Division	CDER/OND/ODEII/DAAAP
Manufacturing Site	*Drug product manufacturing, packaging, labeling, and alternate testing site for drug product microbiological testing:* West-Ward Columbus, Inc. 1809 Wilson Road (b) (4) Columbus, Ohio, 43228, USA FEI: 1510690 *Microbiological testing for release and stability:* (b) (4)
Method of Sterilization	non-sterile, aqueous, non-preserved

Assessment Recommendation: Adequate

Assessment Summary: This drug product is a non-sterile, aqueous, inherently antimicrobial, single-use nasal spray. No significant changes were made in this response to the 28 February 2020 Complete Response Letter (CRL) that affect the sterility assurance of the drug product.

Submissions being assessed:

Document(s) Assessed	Date Received
Seq-0023 (SDN 24)	29 October 2020

Highlight Key Issues from Last Cycle and Their Resolution: No sterility assurance issues were identified in the last cycle (cycle 001).

Remarks: On 3 September 2019, Seq-0010, Insys Therapeutics, Inc (the original applicant) notified the Agency that the ownership of this NDA was transferred to Hikma Pharmaceuticals USA Inc (Hikma).

On 10 September 2019, Seq-0014, Hikma notified the Agency that the drug product manufacturing facility would be moved from the Insys Therapeutics Round Rock, Texas site to the Hikma, West-Ward, Columbus, Ohio site in a like for like site transfer.

At the end of the first review cycle (001), the applicant had not yet provided data from exhibit batches manufactured at the newly proposed Hikma, West-Ward manufacturing facility in Columbus, Ohio. Stability data from exhibit batches manufactured at the Hikma, West-Ward, Columbus, Ohio facility were provided in Seq-0023, 29 October 2020, and are reviewed here.

In Seq-0023, 29 October 2020, the applicant provided a response to the 28 February 2020 CRL. No product quality microbiology information requests were sent to the applicant in the CRL and none of the responses to information requests sent in the CRL by other disciplines impact the sterility assurance of this drug product.

Concise Description of Outstanding Issues: N/A

Supporting Documents: The DMA review of the first review cycle for NDA 212045 (file name: N212045MR01.pdf, dated 28 October 2019) was determined to be adequate and supports the sterility assurance of the Naloxone Nasal Spray drug product.

Product Quality Microbiology

P.5 CONTROL OF DRUG PRODUCT

There is no change to the specification. The information provided below is for reference.

P.5.1 SPECIFICATION

Microbial limits:

Total aerobic microbial count: (b) (4) cfu/g
Total combined yeast/mold count: (b) (4) cfu/g
Specified microorganisms: Absence of *E. coli, P. aeruginosa, S. aureus*, and *B. cepacia* complex (BCC) per (b) (4)

P.5.2 ANALYTICAL PROCEDURES

Microbial Limits Testing: USP<61>, USP<62>

P.8 STABILITY

Note to reviewer: Data from stability studies performed for exhibit batches manufactured at the Insys Therapeutics Round Rock, Texas facility (batches 10281017, 10291017, 10301017, 10701218, 10711218, 162342, 162343) and data from stability studies performed for exhibit batches manufactured at the Hikma, West-Ward, Columbus, Ohio facility (batches AB0418A, AB0419A, AB0420A) were provided in the Seq-0023 submission. Only information relevant to the exhibit batches manufactured at the Hikma, West-Ward, Columbus, Ohio facility is reviewed here.

P.8.1 STABILITY SUMMARY AND CONCLUSION:

There is no proposed change to the shelf-life. A 24-month shelf-life at 25°C is proposed for the drug product.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT:

The applicant provided document ST-COM-1927-8-20-00, dated 21 September 2020 describing the post-approval stability commitment and protocol. The applicant commits to continue the stability studies for drug product batches manufactured at Insys Therapeutics and for the three registration drug product batches manufactured at Hikma Columbus, Ohio (AB0418A, AB0419A, AB0420A). Thereafter, one lot per calendar year for the drug product will be placed under long-term stability conditions (described in the tables below). The results of stability studies will be reported to the Agency in annual reports. The microbial limits specification is the same for stability as for drug product release.

Long-term storage condition (upright and inverted storage): 25°C/60% RH

Test	Time (months)							
	Initial	3	6	9	12	24	30	36
Microbial Limits	+				+	+	+	+

Long-term storage condition (upright and inverted storage): 5 ± 3°C

Test	Time (months)							
	Initial	3	6	9	12	24	30	36
Microbial Limits	+	+			+	+	+	+

Assessment: *Adequate*

P.8.3 STABILITY DATA: All three registration batches (AB0418A, AB0419A, AB0420A) manufactured in March 2020 at the Hikma, West-Ward Columbus, Ohio facility were placed in stability studies. Data from the first 3 months of stability studies were provided by the applicant. Microbial limits testing time points have not been reached.

Assessment: *Adequate*

R REGIONAL INFORMATION

Executed Batch Records: Executed batch records were provided for the drug product manufactured at the Hikma, West-Ward, Columbus, Ohio facility (AB0418A, AB0419A, AB0420A). All three exhibit batches met the drug product release specification and were placed in stability studies.

> *Note to reviewer:* Exhibit batches AB0418A and AB0420A were manufactured with 20% ethanol (proposed for commercial production of the drug product). Exhibit batch AB0419A was manufactured with (b) (4)% ethanol (not proposed for commercial production of the drug product).

Assessment: *Adequate*

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: Julia Marré, PhD, Microbiologist, 11 December 2020

Secondary Assessor Name and Date: Neal Sweeney, PhD, Microbiology QAL, 11 December 2020

Neal Sweeney

Digitally signed by Neal Sweeney
Date: 12/11/2020 02:56:20PM
GUID: 508da70c00028f5119acd77351f33159

Julia Marre

Digitally signed by Julia Marre
Date: 12/11/2020 02:45:09PM
GUID: 5ac654d90075eaa6b93887b3adda09f0

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 3/29/2021 04:34:38PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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/

VALERIE R AMSPACHER
03/29/2021 04:39:32 PM

INTEGRATED QUALITY ASSESSMENT FOR NDA 212045

Contents

Executive Summary and ATL Review

NDA 212045

RECOMMENDATION

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

NDA 212045
Assessment 1

Drug Product Name	Naloxone Nasal Spray
Dosage Form	Spray
Strength	8 mg
Route of Administration	Nasal
Rx/OTC Dispensed	Rx
Applicant	Insys Development Company, Inc.
US agent, if applicable	n/a

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA/SD 01	30-APR-2019	All
Amendment /SD 02	09-MAY-2019	DS
Amendment/ SD 08	17-JUL-2019	DS, Process and Facility
Amendment/ SD 09	06-AUG-2019	DS, DP, Process and Facility
Amendment/ SD 11	03-SEP-2019	Process and Facility
Amendment/ SD 12	04-SEP-2019	Process and Facility
Amendment/ SD_13	05-SEP-2019	DS
Amendment/ SD 14*/15	10-SEP-2019	DS, Process and Facility
Amendment/ SD 16	20-SEP-2019	Process and Facility
Amendment/ SD_17	18-OCT-2019	DP
Amendment/ SD		

*** Updated 356h to reflect new owner of the NDA, with no change in facilities**

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sam Bain, PhD	Donna Christner, PhD
Drug Product	Jizhou Wang, PhD	Julia Pinto, PhD
Manufacturing	Yeung Chan	Yaodong (Tony) Huang
Microbiology	Julia Marre, PhD	Denise Miller
Biopharmaceutics	N/A	N/A

Regulatory Business Process Manager	Anika Lalmansingh, PhD	
Application Technical Lead	Venkateswara Pavuluri	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA is NOT APPROVABLE from quality perspective for the following reasons:

Due to change of ownership of the NDA after filing, new owner decided to change drug product manufacturing and primary and secondary packaging facility during the review cycle, from Insys site to West-Ward Columbus, Ohio. West-Ward Columbus site in Ohio is also the release and stability testing site for drug product, and control and release of all components (API, excipients, and packaging items). Given this is a high-risk drug-device combo product and site transfer activities include transport of equipment, IQ/OQ/PQ of manufacturing line, and production of 3 new exhibit batches, a PAI was requested by OPMA and CDRH reviewers. However, as the new facility will not be ready for the inspection until June 30, 2020, **a complete response has been recommended by OPMA/OPQ and CDRH reviewers**.

Extractable and leachable risks from manufacturing equipment and the container closure system in to the drug product has not been sufficiently addressed, and hence **OPMA and ONDP drug product reviewers recommended a complete response**.

Satisfactory Pre-approval inspection of new manufacturing facility for drug product and device assembly /packaging and resolution of all other outstanding quality deficiencies listed below is required before this NDA may be approved.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Naloxone nasal spray, 8 mg/0.1 mL is a single-use, drug-device combination product intended for use in the community. The Applicant proposes using the commercially available nasal spray device from (b) (4) that delivers 100 µl (8 mg of naloxone HCl) intranasally for use in patients of all ages, both adults and children. The Applicant relied on the previous findings of efficacy and safety for the reference product, Narcan (NDA 016636), which is approved for known or suspected opioid overdose.

The NDA ownership has changed from Insys to Hikma during the review cycle. With transfer of ownership, the new applicant (Hikma) also proposed to change the drug product manufacturing site, requiring a pre-approval inspection (PAI) of the new site by the Agency. However, as the new facility identified by the current

applicant during the review cycle will not be ready for the inspection until June 30, 2020, a complete response has been recommended by the Agency, from Quality (CMC) perspective.

Proposed Indication(s) including Intended Patient Population	1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. 2. Immediate administration as emergency therapy in settings where opioids may be present.
Duration of Treatment	As needed in suspected opioid overdose cases.
Maximum Daily Dose	16 mg (as proposed by the applicant)
Alternative Methods of Administration	Injection, intramuscular and intravenous with dose adjustment

B. Quality Assessment Overview

Drug Substance: Adequate

USP has a monograph for the drug substance, Naloxone Hydrochloride. For the drug substance CMC, the applicant has referenced DMF [redacted] (b) (4), which has been found adequate by the Agency. The NDA includes the applicant's controls of the drug substance, which include compliance with USP monograph and ICH guidelines, and critical aspects of the DMF holder's specification. Based upon the current adequacy of the DMF and the information provided in the NDA, the drug substance manufacturing process, characterization, shelf-life specification, container closure system and stability are satisfactory.

The supplier [redacted] (b) (4) has indicated a retest period of [redacted] (b) (4) for the drug substance, which has been found adequate; DMF review dated 25-OCT-2019.

Safety Limits of Impurities in the Drug Substance as per ICH Guidelines:

MDD*	ICH Q3A RT	ICH Q3A IT	ICH Q3A QT	ICH M7 TTC
16 mg	0.05%	0.10%	0.15%	[redacted] (b) (4) µg/day)

* Confirmed by the OND clinical reviewer, I. Khachikyan, 22-JUL-2019.

Drug Product: Inadequate

Naloxone Nasal Spray finished drug product is a nasal spray formulation supplied in a unit dose nasal spray container. The spray device delivers about 100 µL of Naloxone Nasal Spray, in turn delivering 8 mg of Naloxone Hydrochloride per spray. It is used for known or suspected opioid overdose.

A ternary solvent system (water/ethanol/propylene glycol) was selected as a vehicle to achieve desired solubility of Naloxone Hydrochloride, and

[redacted] (EDTA) was selected as an appropriate [redacted] agent to ensure the physical and chemical stability of Naloxone Hydrochloride in the Nasal spray. Alcohol (ethanol) was used to improve nasal drug permeability. All excipients of Naloxone Nasal Spray formulation have been controlled according to USP/NF monographs except HCl/ NaOH [redacted] which are dilute solutions prepared from USP/NF compendial grade HCl and water used for pH adjustments.

The quality of the drug product has been controlled as per USP General Chapters, ICH Q3B and US FDA Guidance for Industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products -Chemistry, Manufacturing, and Controls Documentation (CEDR, 2002)*. Sponsor has agreed to revise some specifications as per Agency's requests and will provide updates around August of 2020, which is far after the PUDFA date of February 28, 2020. Overall the drug product was quite stable and did not show any trend except significant fluctuation for edetate disodium dihydrate (EDTA) across different timepoints and different batches. Sponsor has committed to investigate the root reasons for the variation and re-validate the analytic methods. However, the planned date to provide the required information is, August of 2020, which is far after the PUDFA date of February 28, 2020. Based on the 6 months of accelerated and 12 months of real-time stability data, a shelf life of 24 months has been proposed when stored at 20-25°C (68-77°F) with excursions permitted to 40°C (104°F) and to 5°C (41°F).

Controlled extractable studies performed on component of the primary CCS are not adequate due to selection of inappropriate sample preparation methods and narrow pH range of the buffer solution. The leachables studies are not adequate in term of non-validated analytical methods and lack of analytical methods for [redacted]. Though sponsor has committed to provide the required information upon Agency's requests, the time line is from the May to August of 2020, which falls outside of the PUDFA date of February 28, 2020.

Due to the many unsolved issues listed above, including extractables and leachables studies and the out of trend of EDTA, the quality of the **drug product was deemed inadequate for this review cycle and thus recommended complete response.**

Labeling: Inadequate

Refer deficiencies listed below for the PI, Carton and container labels.

Manufacturing: Inadequate

The drug product manufacturing process operations include [redacted]

and the drug product formulation includes Edetate Disodium Dihydrate (EDTA) [redacted]. No scale up has been proposed [redacted]. IPC specifications for pH, viscosity, and density requested. [redacted]. **Extractable and leachable risks from manufacturing equipment have not been sufficiently addressed.**

The drug substance manufacturing facility has experience manufacturing the API and is currently cGMP compliant and is deemed approvable at this time.

While the drug product facility has experience manufacturing nasal sprays, given this is a high-risk drug-device combo product and site transfer and qualification of entire manufacturing line is yet to be performed, a PAI will be requested upon resubmission.

Biopharmaceutics: Adequate

Biopharmaceutics review activity is not needed for this NDA

Microbiology (if applicable): Adequate

This is a non-sterile, aqueous, non-preserved, single-use, nasal spray drug product; packaged in a unit-dose spray device that delivers the entire contents of the drug product in one spray (single-use). The applicant provided adequate information to support the self-preserving nature, the routine release testing, and the stability testing of the drug product.

The Microbiology review attached below contains information provided in the original submission of the NDA with Insys as drug product manufacturing site. The applicant has not manufactured exhibit batches at the newly proposed, Hikma Columbus, Ohio site and, therefore, there are no executed batch records for this new facility. It is expected that the applicant will provide these documents in the future, as part of a resubmission.

C. Risk Assessment: Risk assessment not complete at this time as the NDA is not approvable from quality perspective

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**

		H, M, or L		Acceptable or Not Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

Due to change in ownership of the NDA after filing, new owner decided to change drug product manufacturing and primary and secondary packaging facility during the review cycle, from Insys site to West-Ward Columbus site in Ohio. West-Ward Columbus site in Ohio is also the designated facility for release and stability testing of drug product, and control and release of all components (API, excipients, and packaging items) of the combination product. Given this is a high-risk drug-device combo product and site transfer activities, including transport of equipment, IQ/OQ/PQ of manufacturing line from original manufacturing site, and production of 3 new exhibit batches occurring during this review cycle, a PAI was requested by OPMA/OPQ and CDRH. However, as the new facility will not be ready for the inspection by ORA until June 30, 2020, a complete response has been recommended by ONDP, OPMA/OPQ and CDRH reviewers.

As the extractable and leachable risks, from both manufacturing equipment and the container closure system, in to the drug product has not been sufficiently addressed, OPMA and ONDP drug product reviewers recommended a complete response.

Satisfactory inspection of the new manufacturing facility for drug product and resolution of all other outstanding deficiencies listed below is required before this NDA may be approved.

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

1. We have following comments regarding the extractables studies:

   a. Different maximum daily doses (MDD) have been used to calculate the AETs for the extractables studies. Specifically, in (b) (4) 2011 report, an MDD of 8 mg/day was used to calculate the AET for volatile, semi-volatile and non-volatile, while in (b) (4) report TTP-IOX-M0083, Doses/day = 4 (8 mg/spray, 32 mg/day) was used

for the calculation of AETs for polar compounds and elemental impurities. Clarify the discrepancies and provide the revised AETs with the correct MDD.

(b) (4)

b. You stated that the profile (b) (4) contained (b) (4) (b) (4) (b) (4) However, we cannot locate the information. Please provide the same.

c. If there is any change in the material composition of the rubber stopper, commit to provide the Routine Extractables Studies as per FDA Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (2002) available at https://www.fda.gov/media/70857/download

2. We have following comments regarding the Leachable studies:
   a. We do not agree with your design for leachables testing following the concept of ICH Q1D "Bracketing and Matrixing designs for the stability testing of new drug substance and products." Potential leachables may decompose to generate secondary leachables over time. Therefore, the full stability protocol should be followed in order to determine the full leachable trend throughout the product life cycle.

   b. You stated that all the Naloxone Nasal Spray samples were stored in horizontal orientation as a worst-case scenario during the stability studies. However, inverted position will maximize stopper/drug product solution contact. Re-run the leachables studies in the inverted position or justify why the horizontal position is the worst-case scenario for leachable determination.

c. In 3.2.P.2.4.10.4. Characterization of Leachables and the original report IOXM0085 report: Semi-Quantitation of Extractables from [redacted] Stoppers, you have adopted an AET of [redacted] µg/mL, which is 100-fold higher than the AET [redacted] used for extractables studies. In addition, 3 of 4 reporting limits for the target leachables [redacted] are much higher than the AET [redacted] µg/mL) as shown in table 9 and table 11 below. Please clarify these discrepancies and provide a revised AET based on a SCT of [redacted] µg/day.

[redacted]

3. The acceptance criterion for "Total Impurities" [redacted] is too wide in the release and stability specification. Tighten the acceptance criterion based on the data trend.

4. Include the acceptance criterion for the potential degradation impurity [redacted] in both release and stability specification as per ICH Q3B. Alternatively provide sufficient batch data to show it is absent in the drug product with validated methods.

5. We acknowledge that [redacted] has been controlled in the vendor's COA for dehydrated ethyl alcohol [redacted] in the formulation, demonstrate that your analytical method can detect [redacted] and [redacted] is absent in the drug product.

6. Regarding method validation, we have following comments:

   a. Provide the forced degradation studies for CH.0103: Assay and Identification of Naloxone in Naloxone Nasal Spray, 8mg/Spray.
   b. Provide system suitability requirements for validation reports CH.0151: Assay of Ethanol by GC-FID, Method CH.0109:

Impurities [redacted] by HPLC, Method CH.0117: Impurity [redacted] by HPLC and CH.0110: Impurity [redacted] by HPLC;

c. Provide a complete method validation report for impurity [redacted]
d. Provide the details for the referenced Report.CH.0046 for Method CH.0109: Method Validation Report for Impurities [redacted] by HPLC method.

7. Regarding your structural assignment for impurity [redacted] we have following comments:

   a. you have assigned impurity [redacted] based on the presence of the signal [redacted] Provide the sources [redacted] on page 4 of Analysis Report: [redacted] and clarify why [redacted] is a diagnostic [redacted].
   b. Since reference standard for [redacted] is not available to verify the structure of impurity [redacted] provide direct spectroscopic evidences for [redacted] impurity [redacted]
   c. If you cannot unambiguously assign the structure of impurity [redacted] we recommend you list the impurity as a specified unknown impurity with RRT in the release and stability specification.

8. Provide the design and materials of construction of the labels used on the primary container for naloxone hydrochloride nasal spray.

9. Provide the vendor COA for [redacted] vial.

10. In 3.2.P.2.2 the stability study results have demonstrated that formulations with EDTA at a concentration of [redacted]% w/w at a pH of [redacted] yielded the most stable formulations with an optimum impurity profile. However, you have adopted a much wider pH range [redacted] for both release and stability specification. Justify the wider pH ranges by providing data to demonstrate the continued stability of the API and Edetate Disodium at higher or lower pHs or revise the pH specification (range) for release and stability, based on the observed values for drug product batches tested thus far.

<u>Other comments (not approvability issues):</u>

11. Add a note that [redacted] is equivalent to 8.0 mg of Naloxone Hydrochloride below the composition table in 3.2.P.1. Description and Composition of the Drug Product.

d. Labeling Deficiencies

1. Include drug established name in the highlights section of PI after the trade name in parenthesis.
2. To comply with FDA Guidance for Industry on "Naming of Drug Products Containing Salt Drug Substances" and USP salt policy, add equivalency statement in section 11 of the PI indicating the strength in terms of the active moiety, i.e. naloxone hydrochloride 8 mg (equivalent to 7.2 mg naloxone) in 0.1 mL. The equivalency statement should also appear on the carton labeling text and if space permits, on container label as well.
3. As per the deficiency #10 identified under drug product section, justify the wider pH range (b) (4) recommended for drug product, by providing data to demonstrate the continued stability of the API and Edetate Disodium at higher or lower pHs, or else revise the pH range specified in the labeling, based on the observed values for drug product batches tested thus far.
4. Provide the amount of alcohol in terms of percent volume of absolute alcohol on Carton Labeling.
5. In Section 16 (HOW SUPPLIED/STORAGE AND HANDLING), if product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."

e. Manufacturing Deficiencies

1. (b) (4) (b) (4) Revise the proposed commercial batch record in 3.2.P.3.3 (b) (4) (b) (4).

2. Leachable and extractable studies are critical to assure no elements or chemical substances are extracted from the manufacturing components under stress conditions to compromise quality of the drug product. We acknowledge you have presented extractable and leachable study results for (b) (4) rubber stopper and leachable screen of aged Naloxone nasal spray DP in 3.2.P.2 to profile potential extractable contaminants.

However, you did not offer any leachable or extractable studies result for all product-contact materials used in manufacturing process to demonstrate no elemental or chemical impurities were extracted from your manufacturing [(b) (4)] under the given process operation conditions. Please provide leachable and extractable data for all the formulation contacting [(b) (4)] components used during the manufacturing process and confirm all formulation contacting [(b) (4)] [(b) (4)] components used in manufacturing of the drug product meet the ASTM standards [(b) (4)]. In addition, please provide a statement of compliance to pertinent CFR sections for indirect food additives for all formulation contacting components used in manufacturing of the drug product.

3. We acknowledge you have proposed to report the values of pH, viscosity, and density during in-process testing of the [(b) (4)] [(b) (4)] solution but without proposing any acceptance specifications for such testing. pH, viscosity, and density are all important critical quality attributes of solution drug product. We therefore recommend you include pH, viscosity, and density as in-process controls per 21CFR 211.110 with acceptance criteria justified with exhibit batch or development studies data. Please revise the in-process controls/specifications in 3.2.P.3.4 and the commercial MBR in 3.2.P.3.3 accordingly. In addition, please provide a side-by-side comparison table listing all in-process tests and their specifications with target and control limits for each stage of the commercial scale manufacturing and exhibit batches, as well as the in-process test results from exhibit batches.

4. Measurement of yield is an estimation of robustness of the process, since deviation investigations are typically performed if yield in the reconciliation section is outside of the specification limits. Your use of reconciliation yield limits for batch reconciliation in commercial MBR are not acceptable as it includes [(b) (4)] and is not an accurate reflection of manufacturing process performance. Per CFR 211.103 and CFR211.186(b)(7), please revise your proposed commercial MBR in 3.2.P.3.3 to include actual yield and actual yield target specification for each unit operation and total production, wherever is applicable.

5. Our field investigator could not complete inspection of the West-Ward Columbus Inc. (FEI: 1510690) manufacturing facility at Columbus, Ohio because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. Please notify us in writing when this facility is ready for inspection.

f. Biopharmaceutics Deficiencies

None

g. Microbiology Deficiencies

None for the original submission. New information from proposed drug product manufacturing site is not available for assessment at the time of this review.

h. Other Deficiencies (CDRH)

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.

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.

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:

   a. 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.

b. 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.
c. Appropriate statistical analysis of these quality data to detect recurring quality problems.
d. Investigations into the cause of nonconformities relating to product, processes, and the quality system.
e. Requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems.
f. 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.
g. Procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications.
h. Requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.
i. 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.
j. Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review.
k. Requires documentation of all CAPA activities.

Application Technical Lead Name and Date:

Venkateswara R. Pavuluri, Ph. D, R. Ph.
30-JAN-2020

APPEARS THIS WAY ON ORIGINAL

Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 1/30/2020 05:21:13PM
GUID: 551eb409003b6d46b8d5dfa7699e4742

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)			Drug substance	Acceptable	25-OCT-2019.	
			Drug product	Adequate	28-NOV-2016	
			Drug product			For (b) (4) glass vial, a completed review of this DMF is not necessary for approval due to the low risks.
			Drug product			For (b) (4) glass vial, a completed review of this DMF is not necessary for approval due to the low risks.
			Drug product /Device			For Spray device, supporting the DMF (b) (4)
			Drug product /Device	Adequate	12-AUG-2015	
			Drug product			For blister packaging, a completed review of this DMF is not necessary for approval due to the low risks.
			Drug product			For blister packaging, a completed review of this DMF is not necessary for approval due to the low risks.

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

Document	Application Number	Description
IND	134954, 126173	Supporting the NDA
NDA	016636	RLD

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A for NDAs			
Pharmacology/Toxicology	N/A			
CDRH-ODE	Completed	Complete response		
CDRH-OC	Completed	PAI pending, Complete response		
Clinical	N/A			
Other	N/A			

115 Pages have been WIthheld in Full as B4(CCI/TS) Immediately Following this Page

(b) (4)

[redacted]

Reviewer's Assessment (Review #1): Adequate

Not applicable

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

(b) (4)

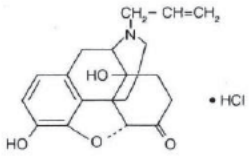
[redacted]

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: naloxone hydrochloride Nasal Spray Established Name: not provided	Not Acceptable
Dosage form, route of administration	Dosage: solution Route: nasal spray	Acceptable
Controlled drug substance symbol (if applicable)	N/A	Acceptable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Nasal Spray: 8 mg of naloxone hydrochloride in 0.1 mL	Acceptable

Conclusion: Not Acceptable with the required data elements as summarized above

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	naloxone hydrochloride	Acceptable
Dosage form and route of administration	nasal spray	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	a single dose of 8 mg of naloxone hydrochloride in 0.1mL.	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	dehydrated alcohol (20% (w/w)) edetate disodium dihydrate, propylene glycol, purified water, and sodium hydroxide/hydrochloric acid to adjust pH	Acceptable
Statement of being sterile (if applicable)	N/A	Acceptable
Pharmacological/ therapeutic class	an opioid antagonist	Acceptable
Chemical name, structural formula, molecular weight	 Chemical name: 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride Molecular formula: C19H21NO4•HCl Molecular weight: 363.84 g/mol	Acceptable

If radioactive, statement of important nuclear characteristics.	N/A	Acceptable
Other important chemical or physical properties (such as pKa, solubility, or pH)	Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform. The pH of the drug product is (b) (4)	Acceptable

Conclusion: Acceptable with the required data elements as summarized above.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Nasal spray	Acceptable
Strengths: in metric system	a single 8 mg dose of naloxone hydrochloride in 0.1 mL intranasal spray.	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear, colorless to yellow solution (not provided)	Not acceptable

Conclusion: Not acceptable with the required data elements as summarized above

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Not provided	Not acceptable
Available units (e.g., bottles of 100 tablets)	supplied as a unit dose spray device that consists of a stoppered glass vial, encased within a spray actuator and container holder. Each Nasal Spray carton contains two individual blisters sealed with a paper backed lidding with a "peel off" feature.	Not acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	a unit dose spray	Acceptable
Special handling (e.g., protect from light, do not freeze)	N/A	Acceptable
Storage conditions	Store TRADENAME Nasal Spray in the blister and cartons provided. Store at 20-25°C (68°F to 77°F), excursions permitted to 40°C (104°F) and to 5°C (41°F).	Acceptable

Conclusion: Not Acceptable with the required data elements as summarized above

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	(b) (4)	Acceptable

2. Labels

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Yes	Acceptable
Net contents (21 CFR 201.51(a))	Yes	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	No	Not Acceptable
Storage (not required)	Yes	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	No	Not Acceptable
Name of manufacturer/distributor	Yes	Acceptable
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Not Acceptable with the required data elements as summarized above

2) Cartons

QUALITY ASSESSMENT
NDA # 212045

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	TRADENAMETM (Naloxone HCl)	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	8 mg nasal spray	Acceptable
Net contents (21 CFR 201.51(a))	Yes	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Yes	Acceptable
Sterility Information (if applicable)	N/A	Not Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	Acceptable
Storage Conditions	Yes	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable
Name of manufacturer/distributor	Yes	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	Yes	Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)	No	Not Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Yes	Acceptable

Conclusion: Not Acceptable with the required data elements as summarized above

Overall Conclusion/summary for labeling: not adequate

Deficiencies on Drug product:

1. Add a note that [redacted] (b) (4) is equivalent to 8.0 mg of Naloxone Hydrochloride below the composition table in *3.2.P.1. Description and Composition of the Drug Product.* The conversion statement must also be included in the labeling (PI and container/carton labels).
2. In **3.2.P.2.2** the stability study results have demonstrated that formulations with EDTA at a concentration of [redacted] (b) (4) w/w at a pH of [redacted] (b) (4) yielded the most stable formulations with an optimum impurity profile. However, you have adopted a much wider pH range [redacted] (b) (4) for both release and stability specification. Justify the wider pH ranges by providing data to demonstrate the continued stability of the API and Edetate Disodium at higher or lower pHs or revise the pH specifications for release and stability to [redacted] (b) (4)

3. We have following comments in regard to the extractables studies:
   a. Different maximum daily doses (MDD) have been used to calculate the AETs for the extractables studies. Specifically, in (b) (4) 2011 report, an MDD of 8 mg/day was used to calculate the AET for volatile, semi-volatile and non-volatile, while in (b) (4) report TTP-IOX-M0083, Doses/day = 4 (8 mg/spray, 32 mg/day) was used for the calculation of AETs for polar compounds and elemental impurities. Clarify the discrepancies and provide the revised AETs with the correct MDD.

(b) (4)

   b. You stated that the profile (b) (4) contained (b) (4) (b) (4) (b) (4). However, we cannot locate the information. Please provide the same.

   c. If there is any change in the material composition of the rubber stopper, commit to provide the Routine Extractables Studies as per FDA Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (2002) available at https://www.fda.gov/media/70857/download

4. We have following comments in regard to the Leachable studies:
   a. We do not agree with your design for leachables testing following the concept of ICH Q1D *"Bracketing and Matrixing designs for the stability testing of new drug substance and products."* Potential leachables may decompose to generate secondary leachables over time. Therefore, the full stability protocol should be followed in order to determine the full leachable trend throughout the product life cycle.
   b. You stated that all the Naloxone Nasal Spray samples were stored in horizontal orientation as a worst-case scenario during the stability studies. However, inverted position will maximize stopper/drug product solution contact. Re-run the leachables studies in the inverted position or justify why the horizontal position is the worst case scenario for leachable determination.
   c. In *3.2.P.2.4.10.4. Characterization of Leachables* and the original report IOXM0085 report: *Semi-Quantitation of Extractables from* (b) (4) *Stoppers,* you have adopted an AET of (b) (4) µg/mL, which is 100-fold higher than the AET

(b) (4) used for extractables studies. In addition, 3 of 4 reporting limits for the target leachables (b) (4) are much higher than the AET ((b) (4) µg/mL) as shown in **table 9** and **table 11** below. Please clarify these discrepancies and provide a revised AET based on a SCT of (b) (4) µg/day.

(b) (4)

5. The acceptance criterion for "Total Impurities" (b) (4) is too wide in the release and stability specification. Tighten the acceptance criterion based on the data trend.

6. Include the acceptance criterion for the potential degradation impurity (b) (4) (b) (4) in both release and stability specification as per ICH Q3B. Alternatively provide sufficient batch data to show it is absent in the drug product with validated methods.

7. We acknowledge that (b) (4) has been controlled in the vendor's COA for dehydrated ethyl alcoho (b) (4) (b) (4) in the formulation, demonstrate that your analytical method can detect (b) (4) and (b) (4) is absent in the drug product.

8. Regarding method validation, we have following comments:
   a. Provide the forced degradation studies for CH.0103: Assay and Identification of Naloxone in Naloxone Nasal Spray, 8mg/Spray.
   b. Provide system suitability requirements for validation reports CH.0151: Assay of Ethanol by GC-FID, Method CH.0109: Impurities (b) (4) by HPLC, Method CH.0117: Impurity (b) (4) by HPLC and CH.0110: Impurity (b) (4) by HPLC;
   c. Provide a complete method validation report for impurity (b) (4)
   d. Provide the details for the referenced Report.CH.0046 for Method CH.0109: Method Validation Report for Impurities (b) (4) by HPLC method.

9. Regarding your structural assignment for impurity (b) (4) we have following comments:
   a. you have assigned impurity (b) (4) based on the presence of the signal (b) (4). Provide the sources (b) (4) on page 4 of *Analysis Report:* (b) (4) (b) (4) and clarify why (b) (4) is a diagnostic (b) (4)

b. Since reference standard for [redacted] is not available to verify the structure of impurity [redacted] provide direct spectroscopic evidences for [redacted] impurity [redacted]

c. If you cannot unambiguously assign the structure of impurity [redacted] we recommend you list the impurity as a specified unknown impurity with RRT in the release and stability specification.

10. Provide the design and materials of construction of the labels used on the primary container for naloxone hydrochloride nasal spray.

11. Provide the vendor COA for [redacted] vial.

II. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]
Secondary Reviewer Name/Date:
Project Manager Name/Date:

Jizhou Wang

Digitally signed by Jizhou Wang
Date: 1/22/2020 12:13:30PM
GUID: 53160853000083c4052c25f3a3cf964a

Julia Pinto

Digitally signed by Julia Pinto
Date: 1/22/2020 01:15:21PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 212045
Drug Product Name	Naloxone Nasal Spray
Strengths	8 mg
Dosage Form	Spray
Administration Route	Nasal
Indication	1) Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. 2) Immediate administration as emergency therapy in settings where opioids may be present.
Applicant Name	Hikma Pharmaceuticals USA Inc.

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate

Process Assessment Recommendation: Inadequate

Assessment Summary:

The drug product manufacturing process operations include (b) (4) (b) (4) (b) (4) No scale up has been proposed. Extractable and leachable risks from manufacturing equipment have not been sufficiently addressed.

The drug substance manufacturing facility has experience manufacturing the API and is currently cGMP compliant and is deemed approvable at this time. While the drug product facility has experience manufacturing nasal sprays, given this is a high-risk drug-device combo product and site transfer and qualification of entire manufacturing line will be performed, a PAI will be requested upon resubmission.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Original NDA (0000)	04/30/2019
Amendment – 8 (0007)	07/17/2019
Amendment – 9 (0008)	08/06/2019
Amendment – 11 (0010)	09/03/2019
Amendment – 12 (0011)	09/04/2019
Amendment – 15 (0014)	09/10/2019
Amendment – 16 (0015)	09/20/2019

Amendment – 17 (0016)	10/18/2019

Highlight Key Issues from Last Cycle and Their Resolution:

- Reprocessing statement not provided

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

- [redacted] (b) (4)
- No leachable and extractable studies
- IPC specifications for pH, viscosity, and density requested
- [redacted] (b) (4)

1. Post-Approval Commitments and Lifecycle Management Considerations

Postmarketing commitments (PMC)?	No
Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
West-Ward Columbus Inc. 1809 Wilson Road, Columbus, Ohio, USA, 43228	1510690	[redacted] (b) (4) (b) (4) drug product manufacturing, packaging, and labeling; drug product release and stability testing; drug product microbiological testing || 356h Status: Active LIQ MSO	Withhold - Not Ready
[redacted] (b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			No Evaluation Necessary

20 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Yeung Chan

Digitally signed by Yeung Chan
Date: 12/13/2019 04:51:34PM
GUID: 589b227e0043a984b5ef04213b12b53e

Yaodong Huang

Digitally signed by Yaodong Huang
Date: 12/14/2019 10:50:17AM
GUID: 5314c51b00004fc086ceeaa91af8e9da

CHAPTER VII: MICROBIOLOGY

Product Information	This is a non-sterile, aqueous, single-use, nasal spray drug product that is indicated in the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. This drug product is packaged in a unit-dose spray device that delivers the entire contents of the drug product in one spray (single-use).
NDA Number	212-045
Assessment Cycle Number	001
Drug Product Name/ Strength	Naloxone Nasal Spray (Naloxone Hydrochloride, USP), 8 mg
Route of Administration	Nasal spray
Applicant Name	Hikma Pharmaceuticals USA Inc.
Therapeutic Classification/ OND Division	CDER/OND/ODEII/DAAAP
Manufacturing Site	*Drug product manufacturing, packaging, labeling, and alternate testing site for drug product microbiological testing:* 1809 Wilson Road (b) (4) Columbus, Ohio, 43228USA FEI: 1510690 *Microbiological testing for release and stability:* (b) (4)
Method of Sterilization	non-sterile, aqueous, non-preserved

Assessment Recommendation: Adequate

Assessment Summary: This drug product is a non-sterile, aqueous, single-use nasal spray. The applicant provided adequate information to support the self-preserving nature, the routine release testing, and the stability testing of the drug product.

Submissions being assessed:

Date Submitted	Date Received	Date Assigned to Reviewer
30 April 2019	30 April 2019	9 May 2019
3 September 2019	3 September 2019	-
10 September 2019	10 September 2019	-

Highlight Key Issues from Last Cycle and Their Resolution: NA

Remarks: On 3 September 2019, Insys Therapeutics, Inc (the original applicant) notified the Agency that the ownership of this NDA was transferred to Hikma Pharmaceuticals USA Inc (Hikma).

On 10 September 2019, Hikma notified the Agency that the drug product manufacturing facility would be moved from the Insys Therapeutics Round Rock, Texas site to the Hikma Columbus, Ohio site in a like for like site transfer. Hikma detailed the following approach overview for the like for like site transfer:

1. Same API source and vendor
2. Same excipients
3. Same primary packaging materials and design
4. Same proposed content of labelling as agreed to by the Agency
5. Supplier qualification status for all materials will be verified
6. Same manufacturing equipment
7. Same packaging equipment
8. Same process flows
9. Same CPPs and control strategy
10. Equipment qualifications will be performed at Hikma
11. Drug product CQAs/specifications will remain the same
12. Same analytical methods (validated) will be used for release and stability testing with intention to perform on-going stability manufactured by Insys at Hikma
13. Engineering/evaluation batches will be manufactured to demonstrate manufacturing capability at Hikma
14. Production of registration/process performance qualification batches (3 batches)
15. Three batches placed on refrigerated (5°C), room temperature (25°C/60% RH), and accelerated (40°C/75% RH) stability conditions. Room temperature samples will be tested for 36 months.
16. Submission of 3 months of stability data to support site transfer

While the applicant has not yet provided data from exhibit batches manufactured at the newly proposed Hikma manufacturing facility, this is acceptable from a microbiology perspective because of the following:

1. The drug product is non-sterile, is single-use, and is self-preserving/bacteriocidal. Therefore, this drug product is considered a low-risk product.
2. The applicant plans to test every batch of drug product for microbial limits per USP<1111> recommendations before the release of the drug product.
3. The Hikma Columbus, Ohio facility is already approved to manufacture another nonsterile product (ANDA 207363, inspected and facility

approved for the manufacture of the nonsterile drug product on 13 June 2018).

This review contains information provided in the original submission of the NDA and contains reviewer notes with discussions of the relevance of the manufacturing site change for specific sections of the review.

Concise Description of Outstanding Issues: NA

Supporting Documents: NA

S DRUG SUBSTANCE: The drug substance is not sterile and the applicant is not requesting reduced release/stability bioburden testing for the final drug product, therefore, a quality microbiology review of the drug substance is not necessary.

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

The drug product is a clear, colorless to yellow solution and is filled into clear glass vials, stoppered, and fitted within a unit-dose nasal spray device. The unit-dose spray device delivers about 100 µl of drug product or 8 mg of Naloxone Hydrochloride per spray.

The composition of the drug product is copied below from the applicant's submission *Section 2.3.P.1 Description and Composition of the Drug Product, p. 1*. This drug product is a hydro-alcoholic formulation.

Table 1: Composition of Hydro-Alcoholic Naloxone Nasal Spray Formulation (Containing 20% Alcohol)

Component	Quality Standard	Function	Composition	
			%, (w/w)[a]	mg/Spray[b]
Naloxone Hydrochloride (b) (4)	USP	Active Ingredient	(b) (4)	
Edetate Disodium, Dihydrate	USP	(b) (4		
Propylene Glycol	USP			
Purified Water	USP			
Dehydrated Alcohol (Alcohol/Ethanol)	USP			
Sodium Hydroxide (b) (4)	In-House Monograph	pH Adjustment Agent		
Hydrochloric Acid (b) (4)	In-House Monograph	pH Adjustment Agent		
Total	-	-		

(b) (4)

Reviewer note: Propylene glycol is also a known preservative agent.

The container closure system consists of an actuator, insert, spray pin, (b) (4) stopper, glass vial, and vial holder. The glass vial and stopper serve as the primary container closure for the drug product. The 19.5 x 6.6 mm glass vial is a clear, colorless Type I glass vial manufactured by (b) (4) (b) (4) and the stopper is (b) (4) rubber stopper manufactured by (b) (4).

Reviewer note on manufacturing site change: Hikma states that the same drug product composition and container closure components will be used for the manufacture of the drug at the Hikma Columbus, Ohio facility. Therefore, the information provided in the original application submission is applicable to the new manufacturing site and is adequate.

Assessment: *Adequate*

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity: The drug product does not rely on the container closure system for microbiological control and, therefore, CCIT is not required for this non-sterile drug product.

Antimicrobial Effectiveness Testing: This drug product is not a multi-dose product and, therefore, AET is not required. However, the applicant performed AET following USP<51> on the drug product to demonstrate the drug product is self-preserving and bacteriocidal. Indicator organisms described in USP<51> were inoculated in drug product at > (b) (4) cfu/mL and incubated at 0, 7, 14, and 28 days. No increase more than 0.5 $\log_{10}$ from the previous value measured was observed for all tested time points and a minimum log reduction of 4.16 was observed for all tested time points after 0 days. Results were provided in *Section 3.2.P.2 Pharmaceutical Development, Att. 42.*

Reviewer note on manufacturing site change: Hikma states that the same drug product composition and container closure components will be used for the manufacture of the drug at the Hikma Columbus, Ohio facility. Therefore, the information provided in the original application submission is applicable to the new manufacturing site and is adequate.

Assessment: *Adequate*
The applicant provided data that demonstrates the drug product is bacteriocidal.

P.3 MANUFACTURE
P.3.1 MANUFACTURERS
Drug product manufacturing, packaging, labeling, and alternate testing site for drug product microbiological testing:
1809 Wilson Road (b) (4)
Columbus, Ohio, 43228USA
FEI: 1510690

Microbiological testing for release and stability:
(b) (4)

Assessment: *Adequate*

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS

(b) (4)

Reviewer note: The applicant did not specify a hold time for the (b) (4) solution (b) (4) however, as this product is self-preserving (see *Section*

P.2.5 Microbiological Attributes), this information will not be requested from the applicant.

Reviewer note on manufacturing site change: Hikma states that the same process flow will be used for the manufacture of the drug at the Hikma Columbus, Ohio facility. Therefore, the information provided in the original application submission is applicable to the new manufacturing site and is adequate.

Assessment: *Adequate*

P.5 CONTROL OF DRUG PRODUCT

P.5.1 SPECIFICATION

Microbial limits:

Total aerobic microbial count: (b) (4) cfu/g
Total combined yeast/mold count: (b) (4) cfu/g
Specified microorganisms: Absence of *E. coli, P. aeruginosa, S. aureus*, and *B. cepacia* complex (BCC) per (b) (4)

Reviewer note on manufacturing site change: Hikma states that the same drug product specification will be used for the manufacture of the drug at the Hikma Columbus, Ohio facility. Therefore, the information provided in the original application submission is applicable to the new manufacturing site and is adequate.

Assessment: *Adequate*

The microbial limits meet USP <1111> recommendations for nasal products.

P.5.2 ANALYTICAL PROCEDURES

Microbial Limits Testing: USP<61>, USP<62>

Reviewer note on manufacturing site change: Hikma states that the same analytical methods (validated) will be used for release of the drug product at the Hikma Columbus, Ohio facility. Therefore, the information provided in the original application submission is applicable to the new manufacturing site and is adequate.

Assessment: *Adequate*

P.5.3 VALIDATION OF ANALYTICAL PROCEDURES

Endotoxins: NA

Sterility: NA

Microbial Limits Testing: [redacted] performed microbial enumeration and specified microorganisms tests per USP<61> and USP<62>. Media growth promotion testing was performed and found acceptable.

For microbial enumeration testing, 1 gram of drug product was filtered, filters were washed, and ≤ [redacted] cfu specified indicator organisms in USP<61> and USP<62> were filtered before the filter was plated and incubated. Test article plates did not exceed a two-fold difference compared to the control plate.

For specified microorganisms testing, ≤ [redacted] cfu *E. coli, P. aeruginosa, S. aureus*, and *B. cepacia* complex (ATCC #25416 and ATCC #39277) were used to inoculate a 1:10 dilution of the drug product (1 g of drug product). Growth was observed in all test and positive control samples and no growth was observed in negative control samples, suggesting that these organisms can be detected using this method.

Reviewer note on manufacturing site change: Hikma proposes to use the Hikma Columbus, Ohio facility as an alternate microbiological testing facility and they commit to using the same analytical methods previously validated for release testing (validated here by [redacted]). Therefore, the information provided in the original application submission is applicable to the new manufacturing site and is adequate.

Assessment: *Adequate*

The proposed bioburden testing method complies with USP<61> and USP<62> and is, therefore, adequate for release testing of the drug product.

P.8 STABILITY

Reviewer note on manufacturing site change: The original stability batches were manufactured at the Insys Therapeutics, Inc facility in Round Rock, Texas. With the transfer of manufacturing to the Hikma Columbus, Ohio facility, the applicant commits to manufacturing another set of exhibit batches (3) and placing these batches in the same stability program detailed in the original application. Therefore, the description of the stability program submitted in the original application is adequate and is described below.

P.8.1 STABILITY SUMMARY AND CONCLUSION

The drug product has a proposed expiration of 24 months at 25°C. The stability program is described below:

5°C ± 3°C: Microbial limits testing at 0, 12, 24, and 36 months
25°C ± 2°C/60%RH ± 5%: Microbial limits testing at 0, 12, 24, and 36 months.
40°C ± 2°C/75%RH ± 5%: Microbial limits testing is not performed.

Reviewer note: This drug product is single-use and, therefore, the applicant was not asked the perform antimicrobial effectiveness testing at the end of the shelf-

life. Additionally, the drug product has a low pH and has demonstrated antimicrobial properties and is, therefore, low risk for microbial proliferation.

Assessment: *Adequate*

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

The applicant commits to continue the stability studies of the ongoing batches as per the study design. The applicant also states that necessary long-term stability studies (25°C with microbial limit testing at 0, 12, 24, and 36 months) will be performed on three full-size process validation batches of the drug product. Additionally, during each year the product is manufactured post-approval, one production batch will be incorporated into the ongoing stability program.

Assessment: *Adequate*

P.8.3 STABILITY DATA

The applicant has not yet manufactured exhibit batches at the Hikma Columbus, Ohio site. This is acceptable and is not cited as a deficiency because the drug product is a low-risk product (non-sterile, single-use, self-preserving/bacteriocidal), the applicant is testing every batch of the drug product for microbial limits per USP<1111> recommendations before the release of the drug product, and the Hikma facility is already approved for the manufacture of another nonsterile drug product (ANDA 207363 inspected and facility approved for the manufacture of the nonsterile drug product on 13 June 2018).

Assessment: *Adequate*

APPENDICES: NA

R REGIONAL INFORMATION

Executed Batch Records for manufacturing site change: The applicant has not manufactured exhibit batches at the Hikma Columbus, Ohio site and, therefore, there are no executed batch records for this facility. This is acceptable and is not cited as a deficiency because the drug product is a low-risk product (non-sterile, single-use, self-preserving/bacteriocidal), the applicant is testing every batch of the drug product for microbial limits per USP<1111> recommendations before the release of the drug product, and the Hikma facility is already approved for the manufacture of another nonsterile drug product (ANDA 207363 inspected and facility approved for the manufacture of the nonsterile drug product on 13 June 2018).

Executed batch records for original manufacturing site: Executed batch records were provided for the 20% alcoholic formulations of the drug product that this ANDA is requesting approval for (lots 10261017, 10271017, 10361017, 10701218). Executed batch records were also provided for the (b)(4)% alcoholic formulation of the drug product that underwent extensive testing during

pharmaceutical development but is not being proposed as the final formulation of the commercial drug product (lots 10281017, 10291017, 10301017, 10711218).

Three lots from each formulation were manufactured at pilot scale (b) (4) and included (b) (4) that is not proposed for the manufacture of the commercial drug product. One lot from each formulation was manufactured at the commercial scale (b) (4) using only the (b) (4) proposed for the manufacture of the commercial drug product.

Reviewer note: The lots manufactured at pilot scale included (b) (4) (b) (4) resulting in a manufacturing process that is more stringent than that proposed for the commercial drug product. However, because one lot from each formulation was manufactured with the same conditions as the proposed commercial drug product and each lot of drug product will be tested for microbial limits per UPS <61> and <62> the applicant will not be asked to re-do the exhibit batches.

Assessment: *Adequate*

Comparability Protocols: NA

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information: The drug product is to be used for one dose and cannot be reused (used drug product is to be discarded after single-use). The drug product is to be stored at 20 – 25°C with excursions permitted to 40°C and to 5°C.

Post-dilution/constitution hold time: NA

Assessment: *Adequate*

Post-Approval Commitments: NA

MICROBIOLOGY LIST OF DEFICIENCIES: NA

Primary Microbiology Assessor Name and Date: Julia Marré, PhD, Microbiologist, 28 October 2019

Secondary Assessor Name and Date: Denise Miller, Sr. Microbiologist, 28 October 2019

Julia Marre

Digitally signed by Julia Marre
Date: 10/28/2019 01:06:14PM
GUID: 5ac654d90075eaa6b93887b3adda09f0

Denise Miller

Digitally signed by Denise Miller
Date: 10/28/2019 01:06:35PM
GUID: 508da7280002a5d546459b998253d1aa

Date	12/16/2019		
To:	Anika Lalmansingh		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	DAAAP
From	Matthew Ondeck OPEQ/OHT3/DHT3C		
Through (Team)	Sarah Mollo, PhD, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) ***Optional**	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	NDA 212045 , Naloxone ICC1900405, ICC1900397 00010719 (Facilities), 00010716 (Premarket)		
Recommendation	**Filing Recommendation Date: 6/4/2019** ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. A PAI inspection is recommended.		
	Mid-Cycle Recommendation Date: 10/4/2019 ☑ CDRH has additional Information Requests, Section 11.		
	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:		

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)	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
None	None	None

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	
Interim Due Dates	**Meeting/Due Date**
Filing	6/6/2019
74-Day Letter	N/A
Mid-Cycle	9/26/2019
Facilities Review Due	11/1/2019
Device Review Due	12/13/2019
Primary Reviews Due	1/21/2019

TABLE OF CONTENTS

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 menifested by respiratory and/or central nervous system. Immediate adminstration as emergency therapy in setting where opioids may be present.
Nasal Spray	Delivery of the Drug Product

2.4. Materials Reviewed

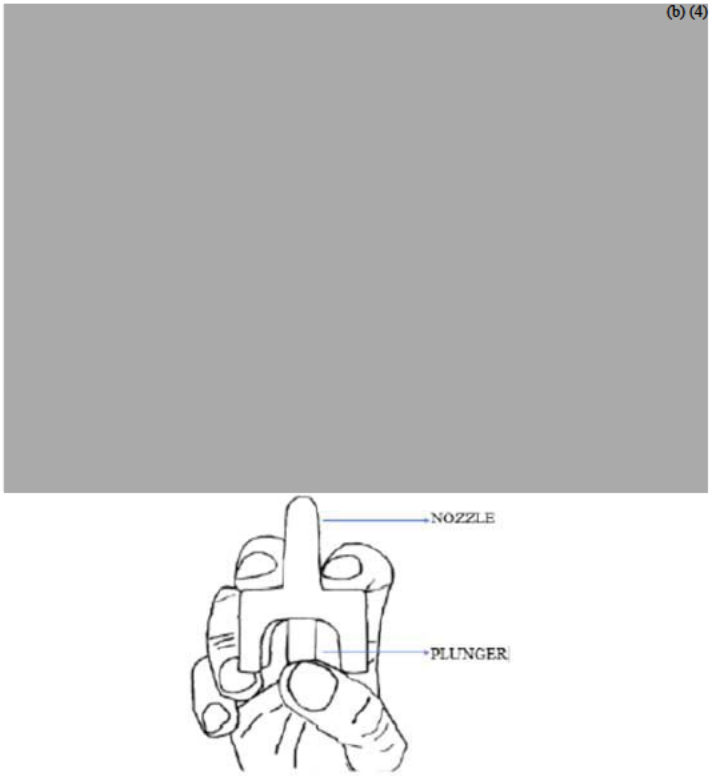
Materials Reviewed	
Document Name	**Location**
container-closure-system	Seq0000.3.2.P.7
ifu-proposed	Seq0000.1
questions-responses	Seq0016.1

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) µL. Upon actuation, devices deliver about 100 µL 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 made of rigid polyvinyl chloride (PVC) film. The blister cavity is sealed (b) (4) (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)	
Primary closure	Stopper (plunger)		
Spray	Actuator		
	Vial Holder		
	Integrated spray pin		
	Spray insert		
	(b) (4)		

The sponsor provides the Letter of Authorization to the Aptar DMF (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 lnsys 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) • Bulk 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]
[redacted]			(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

[redacted] (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:	Drug substance, excipient, packaging component, drug product release and stability testing may be performed at (b) (4) the Wilson Road campus. 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)

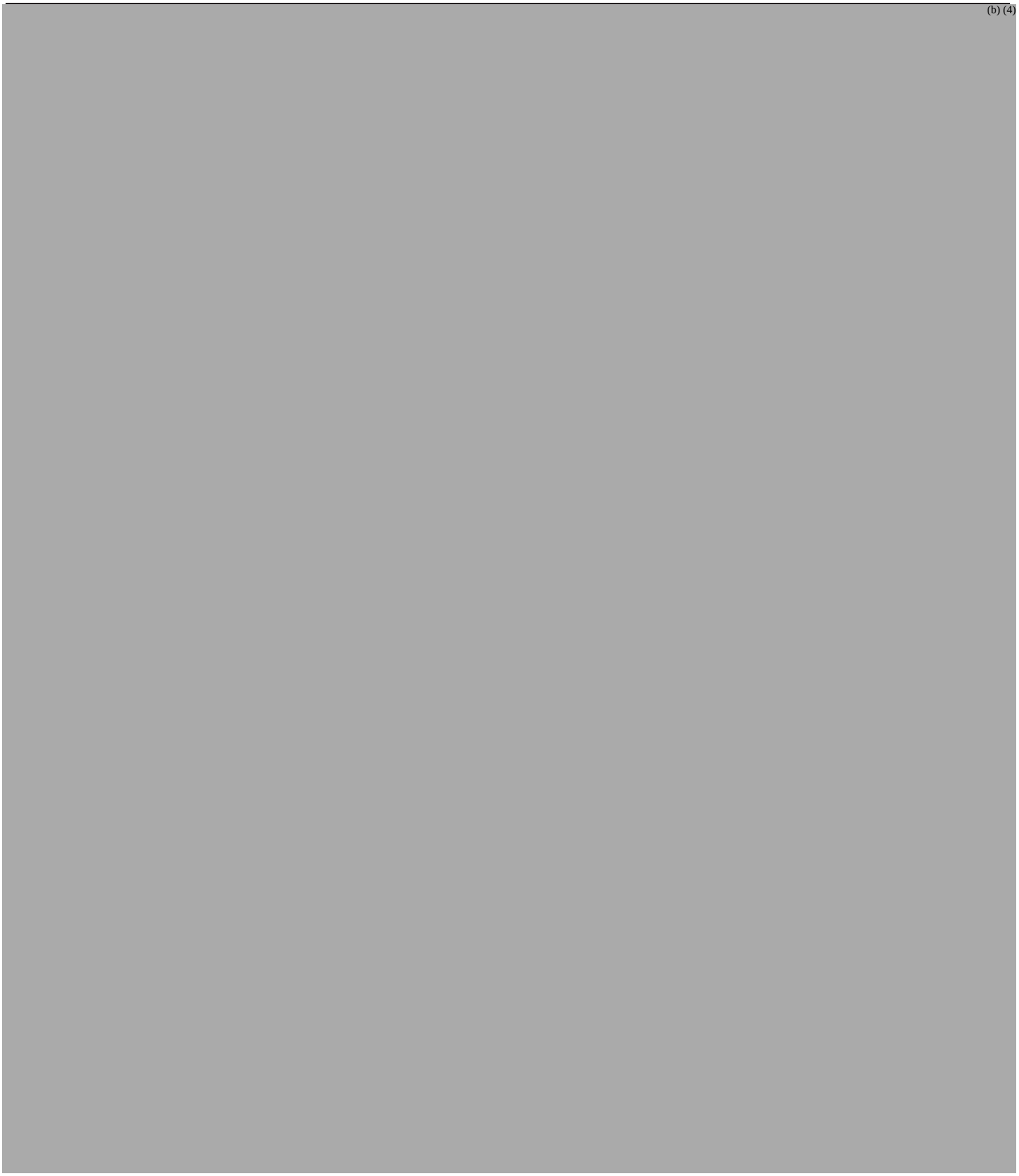
Inspectional History

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:

(b) (4)



(b) (4)

[redacted]

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

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

Inspectional History
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.

Inspection Recommendation:
A pre-approval inspection is NOT required 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.

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

5. LABELING

5.1. General Labeling Review

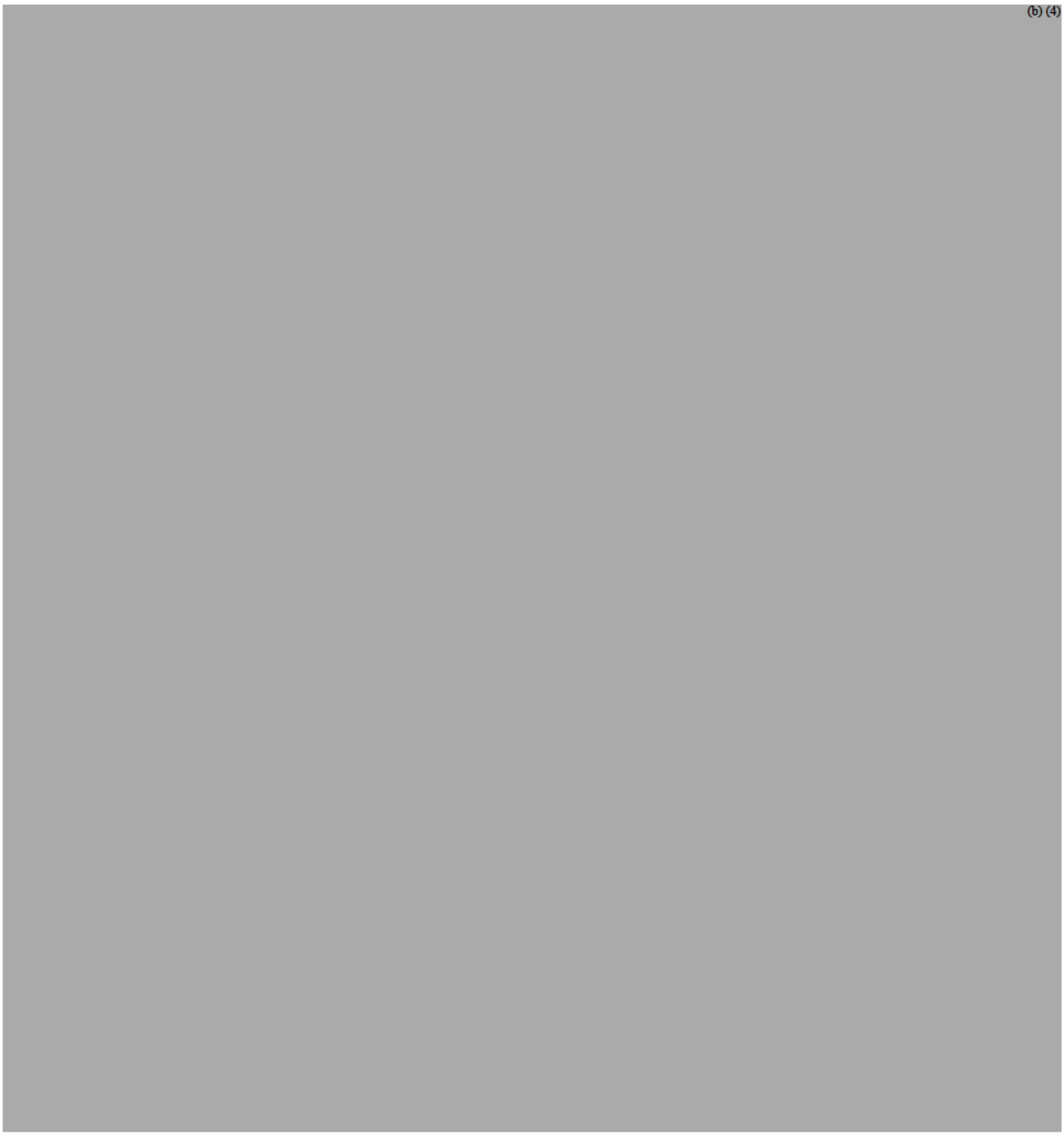
The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

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



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.

- 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 ± 15% of the target weight and none of the individual units is outside ± (b) (4) % of the target weight	CDER Nasal Spray Guidance suggests the following specification for nasal sprays: *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.* Note: 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.
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 (b) (4) determinations from (b) (4) 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) (b) (4) of label claim. If the above acceptance criteria are not met because 2 to 3 of the (b) (4) 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 D90 not less than	
Plume Geometry	The sponsor does not include a specification for plume geometry; however it was measured at release and stability. They state:	While the sponsor provides plume geometry there is no specification to determine acceptability.

	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*	Note: They should provide a specification and ensure that this testing is met at lot release to ensure consistent device performance. See CR deficiencies.
Actuation Force Note: not included in 3.2.P.5.1	The sponsor does not include a true specification for Actuation force: See below 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) (b) (4)	While the sponsor provides actuation force testing after product stability, they do not provide a specification. Note: They should provide a specification and verify that this specification is met. See CR deficiencies.

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.

- 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.

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
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

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.

7.2. Hazard Analysis and Risk Summary Report

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

7.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION

Reviewer Recommendation
The risk analysis is NOT adequate.

APPEARS THIS WAY ON ORIGINAL

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 Acceptable (Y/N)	Validation (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 ± 15% of the target weight and none of the individual units is outside ± (b) (4) % of the target eight NOTE: 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	Yes	Yes	Yes	Yes	Yes
Plume Geometry	NOTE: The sponsor does not include a	No **	No **	No **v	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 ± 15% of the target weight and none of the individual units is outside ± (b) (4) % of the target weight
Methods	Doc: analytical-procedures states: *The test is performed by gravimetric measurement of loss of product upon actuation using an automated actuator.*
Results: Primary Verification	The sponsor provides primary verification testing of dose delivered. This is Seq0000.3.2.p.5.4: doc: batch-analyses

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) units should be within ± 15% of the target weight and none of the individual units is outside ± (b) % of the target weight		Mean= (b) (4) (n= (b) %RSD (b) (4) High = Low =	Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =	Mean= (b) (4) (n= (b) %RSD (b) (4) High = Low =

The mean/high and low dose delivered meet 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.

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.

	Update 12/16/2019: 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: *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.* 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. 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. 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. The spons APPEARS THIS WAY ON ORIGINAL **Table 5:** Spray Content Uniformity/Spray Actuation Content (b) (4)

Device	SAC (By weight)	SCU
S1-C2-D2		
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		

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 ± 15% of the target weight and none of the individual units is outside ± (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 ~ 20 µL, other acceptance criteria can be justified; however, the dose delivered for this device is ~100 µL. 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.
Acceptable:	**No**

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 Testing meets specification. All passed.
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 50% 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

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) containers is not outside (b) (4) of label claim. (See Footnote)*		Mean= (b) (4) (n= (b) %RSD (b) (4) High = Low =	Mean= (b) (4) (n=20) %RSD (b) (4) High = Low =	Mean= (b) (4) (n= (b) %RSD (b) (4) High = Low =

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 D_{90} (90% of droplets) NLT
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	Reviewer Note:

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
Droplet Size Distribution by Laser Diffraction	D_{10} not less than (b) (4) D_{50} not less than D_{90} not less than Span-Report Results		(b) (4)		

	It is noted that the sponsor conducted testing of DSD a [(b) (4)] but only provided a specification for DSD at [(b) (4)] They should state why a specification is not needed at [(b) (4)] cm; 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.
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 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 S1-C2-D1 / [(b) (4)] S3-C1-D2 S3-C9-D1 Average
Conclusions/ Reviewer Comments:	See Reviewer's Comments Above
Acceptable:	☐Yes ☐No

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	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)] The ovality meet the acceptance criteria.
Results: Shelf Life Verification	The sponsor provides the summary results and states that all product met specification; they state:

	In the 20% w/w Alcohol formulation batches [redacted], the minimum (Dmin) dimension ranged from [redacted], the maximum (Dmax) dimension ranged from [redacted] and the ovality ranged from [redacted]. For data at the [redacted], the minimum (Dmin) dimension ranged from [redacted], the maximum (Dmax) dimension ranged from [redacted], and the ovality ranged from [redacted]. No trends were apparent in the data with respect to storage condition, orientation, or time point. 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: [redacted] from Laser beam Device | Dmin (mm) | Dmax (mm) | Ovality S2-C11-D2 S2-C2-D2 S4-C10-D1 Average [redacted] Table 4: [redacted] from Laser beam Device | Dmin (mm) | Dmax (mm) | Ovality S1-C12-D1 S3-C3-D1 S3-C7-D1 Average [redacted]
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 Acceptance Criteria: Sponsor does not define a specification, but they provide testing to demonstrate consistency. A specification should be provided since the sponsor 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.
Methods	The sponsor does not provide the test methods. 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.

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** 40°C/75%RH: Formulation | Lot# | Time point | Orientation | Plume Angle (°) | Plume Width (mm) | Plume Angle (°) | Plume Width (mm) (b) (4) 25°C/60%RH: Time point | Orientation | Plume Angle (°) | Plume Width (mm) | Plume Angle (°) | Plume Width (mm) (b) (4) Naloxone Nasal Spray, 20% alcohol formulation Lot# 162343: T=0 N/A; 1M Upright, Horizontal; 2M Upright, Horizontal; 3M Upright, Horizontal; 6M Upright, Horizontal 25°C/60%RH: T=0 N/A; 3M Upright, Horizontal; 6M Upright, Horizontal; 9M Upright, Horizontal; 12M Upright, Horizontal; 18M Upright, Horizontal Lot# 10261017: T=0 N/A; 1M Upright, Horizontal; 2M Upright, Horizontal; 3M Upright, Horizontal; 6M Upright, Horizontal 25°C/60%RH: T=0 N/A; 3M Upright, Horizontal; 6M Upright, Horizontal They provide plume geometry 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.
Results: Transportation Verification	This was not evaluated after transportation. 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.
Conclusions/ Reviewer Comments:	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 Acceptance Criteria:

	Sponsor does not define a specification, but they provide testing to demonstrate consistency. A specification should be provided since the sponsor 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.
Methods	The sponsor does not provide the test methods. 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.
Results: Primary Verification	See shelf life testing -
Results: Shelf Life Verification	Sponsor provides shelf life testing for plume geometry: (b) (4) 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.
Results: Transportation Verification	This was not evaluated after transportation. 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.
Conclusions/ Reviewer Comments:	See Reviewer's Comments Above
Acceptable:	☐Yes ☒No

Naloxone Nasal Spray Lot	Force to Actuate (kg)			
	Parameter	Release Data	6M 25°C/60%RH	6M 40°C/75%RH
10261017	Avg	(b)		
	Standard Deviation			
10271017	Avg	(b)		
	Standard Deviation			
10281017	Avg	(b)		
	Standard Deviation			
10291017	Avg	(b)		
	Standard Deviation			
10301017	Avg	(b)		
	Standard Deviation			
10361017	Avg	(b)		
	Standard Deviation			

Design Verification:
The design verification is not 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:

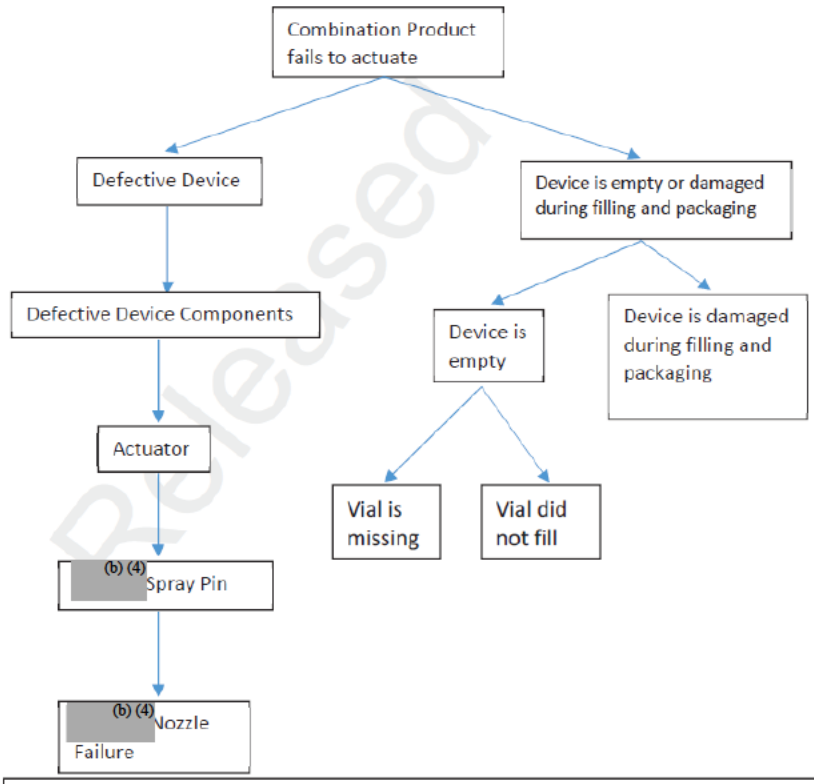
8.2.1. Fault Tree Analysis:

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, needle/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	(b) (4) in 15000 defects will go undetected
	Cannula	Canula moves during plunger piercing	Cannula insertion force is controlled and verified 100% with a sensor	(b) (4) in 15000 defects will go undetected
	Cannula/Spay pin sub assembly	Cannula pierces plunger out of center axis	Cannula/spray pin sub assembly and actuator centering control is verified 100% with sensor	(b) (4) in 15000 defects will go undetected
	Cannula	Cannula does not pierce plunger fully	Occurrence rating of improbable	(b) (4) 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
						(b) (4)
Actuator	Length of base					
	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) dFMA 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 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.

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.

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°C ± 2°C /75%RH ± 5%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
- The sponsor used one lot of the (b)(4)% alcohol and one lot of 20% alcohol. See MC comments
- 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.

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.

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 thathad 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 not adequate.

8.3. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION

Reviewer Recommendation
The design verification is NOT 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 not adequate.

9. HUMAN FACTORS VALIDATION REVIEW

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

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:

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 anlaysis 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	
Inserting the device nozzle into a nostril	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.
Pressing the plunger to release a full dose into the nose	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 *plunger* (since she was actually pushing on the nozzle). When she was unable to depress the *plunger* 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	
Identifying the overdose (checking for response)	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: *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.* Those who checked for signs of an overdose were more literal in their interpretation of: *Do not assume anything. Act as if you came across this person and suspect an opioid overdose situation.*

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: *After the drug is given, is it still necessary to get emergency help by calling 911?* 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	
Moving to a recovery position after administering the dose	Moving the mannequin into the described recovery position Moving the mannequin into a different recovery position Not moving the mannequin into a recovery position	**10** subjects (b) (6) (b) (6) put the mannequin in the recovery position after giving the first dose and after giving the second dose. **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. **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. **6** subjects (b) (6) (b) (6) put the mannequin in the recovery position only after administering both doses. **9** subjects (b) (6) (b) (6) left the mannequin on its back after both doses. **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) 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." Test subject ID (b) (6) would not move a person in case the person had broken bones. Test subject ID (b) (6) did not read the directions at any point in the simulation. 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. Test subjects ID (b) (6) said they did not notice the instructions to move the patient to a recovery position. 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.
Administering another dose using a new unit (if needed)	Administering another new dose Not 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.

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) (4) 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 is 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 facilty 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 (b) (4). Drug product microbiological testing may also be performed at (b) (4) 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: *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,*

		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*:* *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. The description appears appropriate.
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Hikma	**Reviewer Discussion –** The sponsor states: *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.* The description appears appropriate.
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Hikma	**Reviewer Discussion –** Reviewed in Section 12.2.3. *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.* 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

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.

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 release testing activities:	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 Uniforminty	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 controlled through incoming acceptance, in-process control, and/or release testing activities. This should be provided. See CR deficiencies.

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 NOT 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, [redacted] (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:
   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) nits 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 Sp y 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. 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 results 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 appears 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:

    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 request for rationale for statistical sample size. We will provide rationale in our updated reliability for combination product manufactured at WWCI.
b. Additionally, the updated reliability testing will include verification testing of device essential performance requirements.
c. 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 bulk 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) per protocol and for Sequence #8 use of drop height 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.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)

12.1. CR Deficiencies to be Issued to 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.

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.

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:

   a. 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.
   b. 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.
   c. Appropriate statistical analysis of these quality data to detect recurring quality problems
   d. Investigations into the cause of nonconformities relating to product, processes, and the quality system
   e. Requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems
   f. 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

g. Procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications
h. Requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems
i. 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
j. Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review
k. Requires documentation of all CAPA activities

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/

VENKATESWARA PAVULURI
01/30/2020 06:15:46 PM