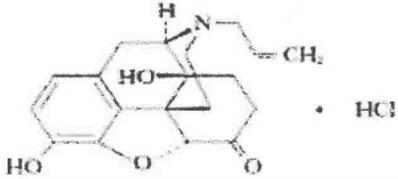


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209862Orig1s000

CHEMISTRY REVIEW(S)

Chemistry Review # 1	1. Division HFD-820	2. NDA Number 205787
3. Name and Address of Applicant Kaleo Inc, 111 Virginia Street, Richmond, VA 23219		4. Supplement Number Date S-7 4/19/2016
5. Name of Drug Evzio ®	6. Nonproprietary Name Naloxone hydrochloride injection auto-injector (NAI)	
7. PA Priority Efficacy Supplement Provides for: 2 mg NAI mfg. at (b)(4) (FEI# (b)(4))		8. Amendment(s) 9/26/2016; 9/14/2016; 8/29/2016; 7/15/2016 and 6/20/2016
9. Pharmacological Category Opioid antagonist	10. How Dispensed Rx	11. Related Documents 5/21/2016 annual report
12. Dosage Form Solution for injection (b)(4)	13. Strength 2 mg NAI (5 mg/ml; 0.4 ml fill)	
14. Chemical Name and Structure EVZIO (naloxone hydrochloride injection, USP) is a pre-filled, single-use auto-injector. EVZIO is not made with natural rubber latex. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure: <div style="text-align: center;">  </div>		
15. Comments: S-7 provides for a 2mg Naloxone hydrochloride injection auto-injector (NAI) for single use as discussed in the pre-NDA meeting 12/8/2014. Same excipients for the injection and same auto-injector components and cartridge components are used for 2 mg NAI and 0.4 mg NAI, CDRH inter-center consult memo dated 9/29/2016 for the auto-injector device has recommended an AP action with a post market requirement (PMR) by Drs. John McMichael and Alan Stevens. OC recommendation for 2 mg NAI is to approve the proposed (b)(4) (FEI# (b)(4)) for drug solution cartridge by Panorama entry dated 10/11/2016. S-7 has provided 3 month stability data for the registration batch of drug solution cartridge (batch (b)(4) mfg. on 2/1/2016 at (b)(4), see page 12) and 6 months stability data for drug solution cartridge (clinical batch D01162 mfg. on 3/30/2015 at (b)(4); see page 25; IND 112292 study KA-900DV-05A; clinical trial lot F0119415BB quantity 105 pcs of assembled auto-injector). (b)(4) decomposition product that limits the shelf life. 0.25 ul of 1% Methylene blue dye solution ingress test method at 40 N forces was used by (b)(4) to detect minute leaks in the container closure system. OPQ/OLDP policy permits 6 months extrapolation for shelf life. Microbiology consult review has recommended an AP action by Panorama entry dated 9/6/2016. There is a categorical exclusion for EA (CFR 25.31b). The drug product is stored (b)(4). S-7 was converted to NDA 209862 on 10/13/2016. See next page.		
16. Conclusions and Recommendations: NDA 205785/S-7 for 2 mg NAI is recommended for approval with 12 mon shelf life. See page 32 for PMR from CDRH.		
17. Name Dr. Pramoda Maturu, Ph.D, Senior Regulatory Review Chemist	Signature Dr. Ramesh Raghavachari, PhD, Branch Chief	Date

Chemist's review notes:

Submission Overall Manufacturing Facility Status

Overall Status	Completion Date	Project Name
Approve	10/11/2016	<u>NDA-205787-SUPPL-7</u>

The sponsor has agreed to provide stability data on 5/18/2016 for 2 mg NAI when it is available. COA for 2 mg NAI clinical batch release is shown on page 24 of this review to justify compliance with release specifications (b)(4) batch D01162A (F0119145BB autoinjector batch) for IND 112292 for the study KA-900DV-05A for dose proportionality. In 2015, cartridge assembly system (CAS) is at (b)(4). There is an on-going leacables study (24 months at 25 C/60%RH) for 0.4 mg NAI to decide for 2 mg NAI but not yet submitted.

Naloxone hydrochloride is readily soluble in water at 5 mg/ml. (b)(4)

Same components for the injection (naloxone hydrochloride USP (b)(4), sodium chloride, hydrochloric acid, water for injection) and same auto-injector components and cartridge components (b)(4)

glass cartridge 0.5 ml, (b)(4) plunger (b)(4)

are used for 2 mg NAI and 0.4 mg NAI, (b)(4)

is located at (b)(4), (b)(4)

(b)(4), 2 mg NAI specification for (b)(4)

decomposition product is NMT (b)(4)% for release and NMT (b)(4)% for shelf life, and there is a (b)(4)

(b)(4) Registration batch

(b)(4) of 2 mg NAI mfg. at (b)(4) complies with (b)(4)

Summary of photostability study data and temperature cycling data for 2 mg NAI and 0.4 mg NAI are provided as per pre NDA meeting, and the degradants are (b)(4), 2 mg NAI compared to 0.4 mg NAI (See page 30 of this review). There is a categorical exclusion for EA (CFR 25.31b) for 2 mg NAI.

Device performance (activation force, volume dispensed, dispensing time, exposed needle length) for 2 mg NAI as a function of time will be evaluated and battery shelf life and (b)(4) shelf life for 2 mg NAI will be evaluated by CDRH consult team. An AP action with a post market requirement (PMR) was made by CDRH. See page 32 for PMR. The sponsor claims that lot to lot variability of dispensing time for 2 mg NAI is corrected by (b)(4)

Different color scheme will be used to differentiate Cartridge carrier assembly for 2 mg NAI and 0.4 mg NAI. 12 mon shelf life for 2 mg NAI is recommended.

Analyte	Nominal Retention Time (Minutes)	Approximate Relative Retention Time	Relative Response Factor ^a
(b) (4)			
Unspecified			(b) (4)
(b) (4)			

Microbiology consult review has recommended an AP action by Panorama entry dated 9/6/2016 by Drs. Daniel Schu and Stephen Langille. OC recommendation for facilities is still pending as of 9/7/2016.

Site name and Address	Responsibilities
(b) (4)	<ul style="list-style-type: none"> • Manufacture • Visual inspection • Quality control testing • Release testing for osmolality and particulate matter
	<ul style="list-style-type: none"> • Release testing • Stability storage and testing

(b) (4)

Same components for the injection (naloxone hydrochloride USP (b) (4), sodium chloride, hydrochloric acid, water for injection) and same auto-injector components and cartridge components (b) (4) glass cartridge 0.5 ml, (b) (4) plunger (b) (4) are used for 2 mg NAI and 0.4 mg NAI, The sponsor has agreed to provide stability data on 5/18/2016 for 2 mg NAI when it is available.

CDRH inter-center consult memo dated 9/29/2016 for the auto-injector device has recommended an AP action with a post market requirement (PMR) by Drs. John McMichael and Alan Stevens. See next page for PMR details. This CDRH memo for S-7 was provided by Dr. Diana Walker on 10/13/2016. S-7 was converted to NDA 209862 on 10/13/2016.

VII. Outstanding Deficiencies

N/A - Recommend Approval of Supplement with PMR listed in Section VIII.

VIII. Post-Market Commitments / Post-Market Requirements

The consulting reviewer proposes the following language for Post-Market Requirements related to combination product reliability.

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:

- a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as $R(t) = x\%$, where t = time and $x\%$ = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning (as described below). The reliability requirements should be verified with a high degree of statistical confidence.
- b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
- c. Describe the use conditions for the product.
- d. Define functionality required for reliability.
- e. Define failure, as it relates to assessing the reliability requirements.
- f. Provide data to verify the reliability requirements. The acceptable endpoints (i.e. acceptance criteria) for this data should be linked to your definition of failure above.
- g. Devices assessed within the reliability verification should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.
 - i. Shipping
 - ii. Aging
 - iii. Storage orientation and conditions
 - iv. Vibration handling
 - v. Shock handling (e.g., resistance to random impacts, such as being dropped).
- h. Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.
 - i. Activation orientation
 - ii. Environmental temperature
- i. Describe how manufacturing controls have been adequately implemented to achieve the reliability specification in the release product lots.

2. Establish a post-market monitoring program for detection and evaluation of under-dose and failure-to-dose events, regardless of cause, and provide periodic reports to the Agency which contains descriptions of each reported event along with results of root-cause and contributing-cause analyses.

Summary: NDA 205785/S-7 for 2 mg NAI is recommended for approval with 12 mon shelf life. See PMR from CDRH listed above.

Page 32

Pramoda
K. Maturu
-S

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K. Maturu
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ou=Ramesh Raghavachari -S
Date: 2016.10.14 10:53:52 -0400

Ramesh
Raghavachari -S

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ou=Ramesh Raghavachari -S
Date: 2016.10.14 10:53:52 -0400

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

Date: October 18, 2016

To: Diana Walker, RPM, CDER/OND/ODE II/DAAAP
Diana.Walker@fda.hhs.gov

Parinda Jani, CPMS, CDER/OND/ODE II/DAAAP
Parinda.Jani@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Diana Walker

Through: Matthew Krueger, Chief, POND, DMQ, OC, CDRH

Matthew C. Krueger -S
2016.10.19 02:40:51 -04'00'

From: Robert Kang, POND, DMQ, OC, CDRH

Applicant: Kaleo, Inc.
111 Virginia St, Suite 300
Richmond, VA 23229
FEI # 3007135538

Application # sNDA205787/S007

Consult # ICC1600357

Product Name: EVZIO (Naloxone autoinjector), 2 mg

Combination Product

Intended Use: Evzio (Naloxone Autoinjector (NAI)) is indicated for (b) (4)

[Redacted text block]

Pre-Approval Inspection: NO

Documentation Review: No Additional Information Required

Final Recommendation: APPROVAL

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of sNDA205787/S007.

PRODUCT DESCRIPTION

NAI is a compact drug delivery system intended for immediate administration of a prescribed dose of naloxone HCl in patients suffering from respiratory depression due to an opioid overdose. The device is a (b) (4) needle-based system that allows a user to deliver the prescribed dose of naloxone HCl into a patient once activated. The needle is fully retracted within the device housing following use. NAI also includes an enhanced labeling feature in the form of an electronic audible and visual prompt system that assists in guiding a user through the injection process (through the use of voice prompts, beeps and LEDs). This electronic prompt system works independently from the mechanical functionality of the naloxone delivery system in the device. Overall dimensions of NAI (height, width, thickness) are 3.4" x 2.0" x 0.64" with an approximate weight of 64 grams.

REGULATORY HISTORY

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

Kaléo Inc. 111 Virginia St, Suite 300 Richmond, VA 23229 FEI # 3007135538	<ul style="list-style-type: none">• Design Control• Design History File (DHF) maintenance• Final product Certificate of Analysis and approval for distribution (final product release)• Annual product review and field alerts
--	---

(b) (4)	<ul style="list-style-type: none">• Quality Control of incoming device components and sub-assemblies• Final product assembly, packaging and labelling• Device performance quality control testing• Maintenance of the Device Master Record and execution of Device History Records
---------	--

	(b) (4)	<ul style="list-style-type: none"> • Quality Control of incoming device components • Assembly of the device components with the Drug Constituent Component to form the Cartridge Assembly • (b) (4) • (b) (4) <p>quality control testing of the Cartridge Assembly</p>
--	---------	--

QS Activity	(b) (4)	Kaleo
Design Controls		
Design Controls, General, 820.30(a)		X
Design and Development Planning, 820.30(b)		X
Design Input, 820.30(c)		X
Design Output, 820.30(d)		X
Design Review, 820.30(e)		X
Design Verification, 820.30(f)		X
Design Validation, 820.30(g)		X
Design Transfer, 820.30(h)		X
Design Changes, 820.30(i)		X
Design History File, 820.30(j)		X
Manufacturing Information		
Quality System Procedures, 820.20(e)	X	X
Purchasing Controls, 820.50	X	X
Production and Process Controls, 820.70	X	
Inspection, Measuring, and Test Equipment, 820.72	X	
Process Validation, 820.75	X	X
Process Validation, 820.75(a)	X	
Receiving Acceptance Activities, 820.80(b)	X	
Final Acceptance Activities, 820.80(d)	X	X
Nonconforming Products, 820.90	X	X

Kaléo Inc. Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted on July 28, 2015. This directed Postmarketing Adverse Drug Experience (PADE) inspection of Kaleo, Inc. (Kaleo hereinafter) was conducted in

accordance with the BLT-DO FY15 work-plan per the "FY 2015: Post Marketing Adverse Drug Experience (PADE) Inspection Request" memo from CDER/Office of Compliance, dated 04/20/2015. No processes were covered as the firm does not manufacture, hold, distribute, test, or package and label any products at this location. The inspection was classified NAI.

(b) (4) Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted on (b) (4). The inspection covered medical device QS requirements and was classified VAI. The inspection covered the assembly and packaging of the Evzio autoinjector. Additionally, CAPA and purchasing controls were evaluated. The inspection resulted in three FDA483 observations. The observations were found to be adequately addressed by the firm according to the April 1, 2014, CDRH OC consult memo.

Inspection Recommendation:

An inspection is required for (b) (4) because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed since (b) (4).

*In considering timeframes, it is recommended that a post market-inspection be conducted within 6 months of approval of the supplement.

MANUFACTURING

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The validation procedures and plans contain or refer to objective and measurable acceptance criteria, and define the criteria and process for re-validation. The procedures provided by the firm have adequately addressed the requirements of 21 CFR 820.75.

RECOMMENDATION

The application for sNDA205787/S007 is approvable from the perspective of the applicable Quality System Requirements.

- Satisfactory desk review of sNDA205787/S007, as it pertains to the Medical Device filing regulatory requirements.
- Acceptability of a post-market inspection of (b) (4)
- A VAI classification recommendation by CDRH/OC of the (b) (4), inspection of (b) (4) after thorough discussions with the (b) (4) investigators and compliance officer.

Robert Kang -S
2016.10.18 15:17:55 -04'00'

Prepared: RKang: 10/18/16
Reviewed: MKrueger: 10/19/2016

CTS No.: ICC1600357
sNDA-205787/S007

Review Cycle Meeting Attendance:
N/A

Inspectional Guidance

Firm to be inspected:

(b) (4)

CDRH recommends the inspection under the applicable Medical Device Regulations.

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), Production and Process Controls (21 CFR 820.70), Inspection, Measuring, and Test Equipment (21 CFR 820.72), and Process Validation (21 CFR 820.75).

REGULATORY STRATEGY

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

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

Primary Contact

Robert Kang, Regulatory Officer
POND/DMQ/OC/CDRH
Office of Compliance, WO66-3438
Phone: 301-796-6614

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

Matthew Krueger, Branch Chief
POND/DMQ/OC/CDRH
Office of Compliance, WO66-3448
Phone: 301-796-5585

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION



GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date: September 26, 2016

To: Diana Walker, RPM
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP),
Office of Drug Evaluation II (ODEII),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

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

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch (GHDB)

Subject: Consult for NDA 205878/S007, ICC1600359

This submission is a supplement to add a 2 mg dose to the previously approved 0.4 mg dose. The Sponsor provided updated validation information, device performance testing and other devices related information. This application has a 6-month PDUFA date and there is a general AC meeting regarding naloxone scheduled for October.

Applicant	Kaleo Inc.
Indication for Use	EVZIO® (naloxone hydrochloride auto injector): The emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Drug / Biologic Constituent	Naloxone
Device Constituent	EVZIO auto-injector AKA 'Naloxone Auto-Injector' (NAI)

Recommendation: Device Constituent Parts of Combination Product Approvable for 2 mg dose with (2) Post-Marketing Requirements for device reliability – Please see Section VIII for draft PMR language.

Digital Signature Concurrence Table	
Reviewer	John C. Date: 2016.09.29 Mcmichael -S 07:45:09 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=130018921 1, cn=Alan M. Stevens -S Date: 2016.09.29 08:09:15 -04'00'

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VIII. Post-Market Commitments / Post-Market Requirements 32

IX. Recommendation 33

I. Purpose / Background

CDER/OND/ODEII/DAAAP has requested CDRH/ODE's assistance in reviewing the EVZIO autoinjector in the context of the newly proposed 2 mg dose. The Sponsor submitted functional testing and stability data in support of the new, higher dose (previously approved for 0.4 mg). This memo serves as a review of the device constituent review of the combination product in the context of the supplement for the addition of the new 2 mg dose.

On December 8, 2014 CDRH/ODE was part of a face-to-face pre-sNDA meeting with the Sponsor in which the Agency and the Sponsor discussed written responses that had been delivered to the Sponsor prior to the meeting. The following are written responses provided by CDRH/ODE relevant to the review of the device constituent parts of the combination product for the sNDA:

Question 6:

Does the FDA agree that the stability program can be conducted [REDACTED] (b) (4) [REDACTED] ?

Agency Response:

No, we do not agree. Evaluate at least one batch of the finished product (device). Include an evaluation of the activation force, volume dispensed, dispensing time, and exposed needle length in the finished product (device) stability protocol.

Question 7:

Does the FDA agree that the sNDA can be reviewed based on submission of all current Evzio stability data and the stability data of 6 months stability of NAIHP?

Agency Response:

The expiry will depend on the data provided. Additional data may be required during the review cycle depending on the stability trends.

Question 10:

Assuming that no differences in stability trends are observed, does the FDA agree the proposed shelf life for NAI [REDACTED] (b) (4) [REDACTED] ?

Agency Response:

No, we do not agree. The proposed higher concentration may influence the stability behavior in comparison to the approved drug. Consequently, the expiry will be based on evaluation of the stability data.

Question 11:

Does FDA agree that NAI-HP finished product does not require a separate registrational stability study and that annual stability lot is adequate to monitor stability trends of NAI-HP?

Agency Response:

We require additional information regarding your proposed separate registrational stability study in order to fully comment. However, the submitted stability studies should be completed and the data provided via annual report. A post-approval commitment should be provided to submit stability data for lots manufactured each year.

Discussion:

The Sponsor clarified that they will conduct stability studies for three lots of cartridges containing drug product and one lot of devices (finished product) for the supplemental NDA submission. The Sponsor agreed to put one lot of marketed product on stability each year postapproval. The Agency agreed with the Sponsor's proposal.

Question 12:

Does the FDA agree [REDACTED] (b) (4)

Agency Response:

No, we do not agree. [REDACTED] (b) (4)

Question 13:

Does the FDA agree with the validation strategy for the FDA label inspection module and the RTS?

Agency Response:

You have indicated that revalidation of the specific module for FDA label inspection will be conducted under a separate protocol while the final validation will be performed under process performance qualification (PPQ). The proposed approach appears acceptable. Provide the results of the validation activities for review upon completion. The acceptability of the validation data is subject to review.

During the December 2014 meeting it was agreed upon by the Agency and the Sponsor that the Sponsor would perform a PK study using the final finished to-be-marketed combination product.

It is important to note that while there were no specific comments made to the Sponsor in regards to the reliability of the combination product, the Agency believes that reliability must be established for this product due to its life-saving indication. CDRH/ODE believes that while this information should have been requested either pre- or post-market for the original NDA application, it is still rationale to request this information under this supplement due to the importance of the information as well as its impact on the safety considerations in regards to the product. This thinking is in line with previous reviews of single-use, emergency use combination products for Naloxone and other emergency use drug products.

II. Administrative

Documents Reviewed:

Document Title	Document Number	Date -Version	Location
Device Product Requirements Specification	IJ-200DI-03O	01/24/2013 – Version 4	GSR Sequence 0010 / Section 3.2.P.7
Stability Summary and Conclusions	N/A	04/19/16	Sequence 0080, 3.2.P.8

Auto-Injector – QS – (b) (4) –Overall Summary Report for Addition of NAI-HD Validation	FPCL-SR-2015-0017	04/19/16	Sequence 0080, 3.2.P.7
Auto-Injector - Release Test Procedures	N/A	04/19/16	Sequence 0080, 3.2.P.7
Auto-Injector – (b) (4) – Differentiation Test of the Evzio Products	N/A	04/19/16	Sequence 0080, 3.2.P.7
Auto-Injector – Shelf- life Stability and Expiration Dating	N/A	04/19/16	Sequence 0080, 3.2.P.7
Pre sNDA – Type B – Meeting Minutes - 23 Dec 2014	N/A	12/23/15	DARRTS
Response to FDA Request for Information – Device – 05 Aug 2016	N/A	08/11/16	Sequence 0101, 1.11.1
Response to FDA Request for Information – Quality CDRH	N/A	09/23/16	Sequence 0109, 1.11.1

CDRH Review Team:

Team Member	Role
John McMichael (CDRH/ODE/DAGRID/GHDB)	Lead Reviewer – Biomedical Engineer

III. Device Description and Performance Requirements

The Device Constituent Component of NAI is a compact, user-actuated, (b) (4) auto-injection system that delivers 0.4 mg or 2.0 mg naloxone hydrochloride injection, USP (1 mg/mL) through a needle into the patient once activated. The needle is fully retracted within the device housing following use.

In addition to labels that provide written instructions for use, NAI includes an enhanced instructions-for-use feature in the form of an electronic prompt system (also referred to as the "Intelliject Prompt System (IPS)") that provides audible instructions for use and visual cues to assist in guiding the user through the injection process.

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Units, mg, increments, etc.)	
Environments of use	Any
Storage conditions and expiry	15°C to (b) (4) Shelf life is 2 years
Graduation marks / fill lines	N/A
Preparation and administration (describe all that are applicable) <ul style="list-style-type: none"> • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc. 	Step 1: Remove Outer Case Step 1a: Interactive System turns on and 1st audible instruction given/LED(s) light up Step 2: Remove Safety Guard/Needle Sheath Step 2a: 2nd audible instruction given/LED(s) light up Step 3: Push NAI base against patient's injection location Step 3a: Base moves upward, activating device, inserting needle, then injecting Naloxone Hydrochloride Step 3b: Final audible instructions given/LED(s) light up Step 3c: Needle retracts back into device housing Step 4: User removes NAI from patient's injection location
Safety Features <ul style="list-style-type: none"> • Needle safety 	(b) (4) (b) (4) NAI shall meet requirements for sharps injury prevention in accordance with ISO-11608 requirements.
Electronics / Data transmission <ul style="list-style-type: none"> • Display • Control functions • Data transmission technology • Data being transferred 	NAI interactive system shall meet IEC 60601-1-2 standard. NAI shall be free from defects when subjected to conditions specified in ISO 11608 section 11.1.3.
Material composition of injector	NAI shall include patient contacting materials that meet ISO 10993-1 biocompatibility requirements.

IV. Design Control Review

A. Design Review Summary

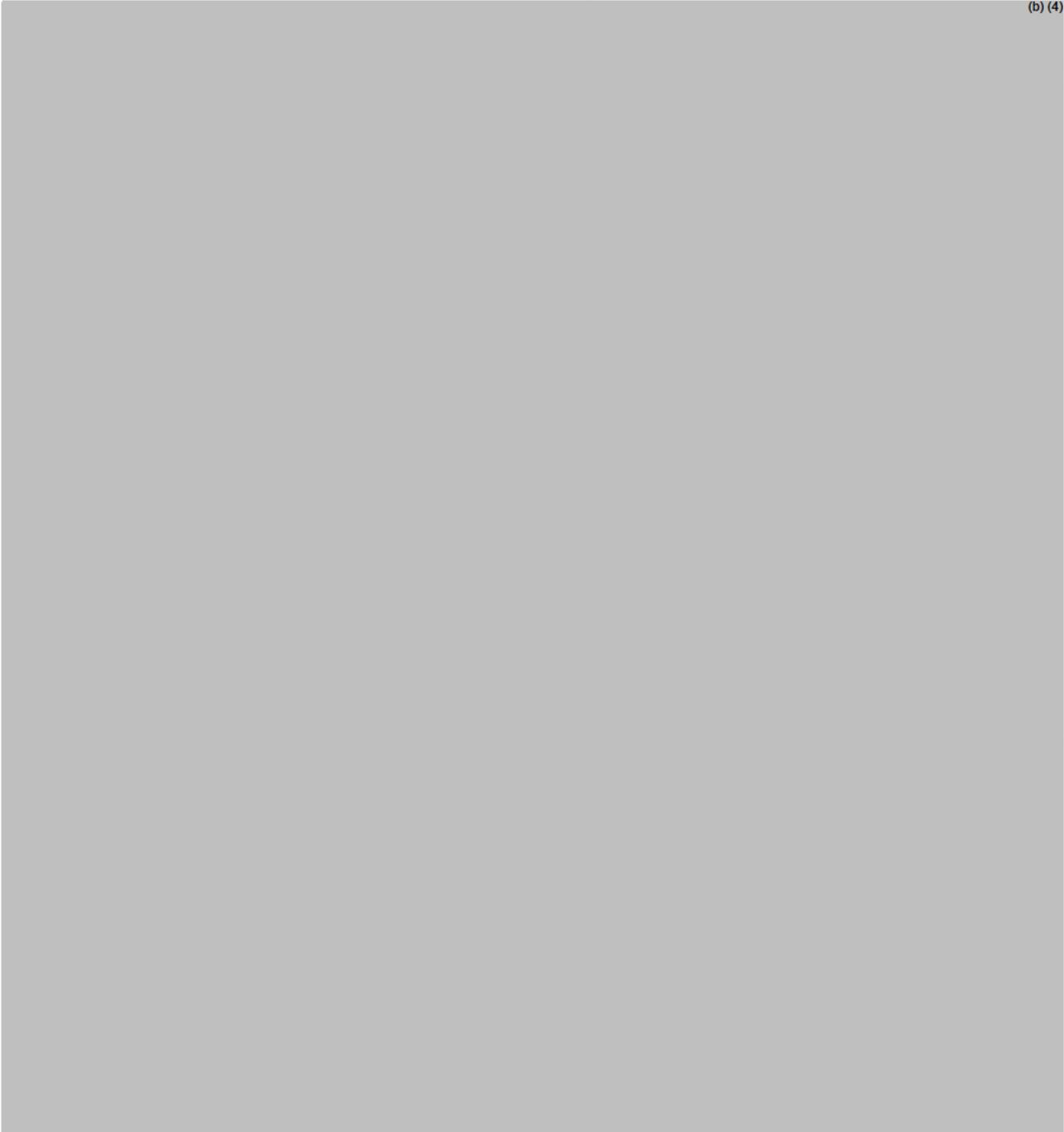
The Design Controls of the Naloxone Auto-Injector was reviewed and established to be adequate under the original NDA application NDA 205787. (b) (4)

This supplement includes no changes to the design controls of the device constituent parts of the combination product, however due to the newly proposed dosage of 2 mg Naloxone, performance testing was required to re-verify the essential performance requirements of the device with the higher dosage form. It should be noted that the deliverable volume of the auto-injector remains the same for both dosage forms.

The Sponsor submitted updated stability testing for the 2 mg combination product and it was observed that a design change was made to correct a dispensing time failure with the device constituent. More information was requested regarding this design change.

The lead reviewer discovered that no post-market requirement of reliability was implemented under the original NDA approval for this combination product. Due to the emergency use of this device the lead reviewer will recommend a post-market requirement of reliability analysis and study for the combination product. This requirement is consistent with reliability requirements of other emergency use Naloxone drug-delivery systems.

(b) (4)



E. Labeling

The following is the currently approved labeling for the 0.4 mg dosage strength with the same device constituent:

<p style="text-align: center;">-----DOSAGE AND ADMINISTRATION-----</p> <ul style="list-style-type: none"> • EVZIO is for intramuscular or subcutaneous use only. (2.1) • Seek emergency medical care immediately after use. (2.1) • Administer EVZIO to adult or pediatric patients into the anterolateral aspect of the thigh, through clothing if necessary. (2.2) • Additional doses may be administered every 2 to 3 minutes until emergency medical assistance arrives. (2.2) • In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering the dose. (2.2) • If the electronic voice instruction system does not operate properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on the flat surface of its label. (2.1) <p>2.1 Important Administration Instructions</p> <ul style="list-style-type: none"> • EVZIO is for intramuscular and subcutaneous use only. • Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of EVZIO and the <i>Instructions for Use</i>. • Seek emergency medical care immediately after use. Since the duration of action of most opioids exceeds that of naloxone hydrochloride, and the suspected opioid overdose may occur outside of supervised medical settings, seek immediate emergency medical assistance, keep the patient under continued surveillance, and administer repeated doses of EVZIO as necessary. Always seek emergency medical assistance in the event of a suspected, potentially life-threatening opioid emergency after administration of the first dose of EVZIO. • Additional doses of EVZIO may be required until emergency medical assistance becomes available. • Do not attempt to reuse EVZIO. Each EVZIO contains a single dose of naloxone. • Visually inspect EVZIO through the viewing window for particulate matter and

discoloration prior to administration. Do not administer unless the solution is clear and the glass container is undamaged.

(b) (4)

- EVZIO must be administered according to the printed instructions on the device label or the electronic voice instructions (EVZIO contains a speaker that provides voice instructions to guide the user through each step of the injection). **If the EVZIO electronic voice instruction system does not operate properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on its label.**

- Once the red safety guard is removed, EVZIO must be used immediately or disposed of properly. Do not attempt to replace the red safety guard once it is removed. Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers (b) (4) naloxone hydrochloride injection, and retracts the needle fully into its housing. Post injection, the black base locks in place, a red indicator appears in the viewing window, and electronic visual and audible instructions signal that EVZIO has delivered the intended dose of naloxone hydrochloride and instructs the user to seek emergency medical attention.

Administration Instructions

Instruct patients and their family members or caregivers about the following important information:

- EVZIO is user actuated and may be administered through clothing [e.g., pants, jeans, etc.] if necessary.
- Inject EVZIO while pressing into the anterolateral aspect of the thigh. In pediatric patients less than 1 year of age, pinch the thigh muscle while administering EVZIO.
- Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers the naloxone, and retracts the needle fully into its housing. The needle is not visible before, during, or after injection.
- Each EVZIO can only be used one time.
- If the electronic voice instruction system on EVZIO does not work properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on its label.
- The electronic voice instructions are independent of activating EVZIO and are not required to wait for the voice instructions to be completed prior to moving to the next step in the injection process.
- Post-injection, the black base locks in place, a red indicator appears in the viewing window and electronic visual and audible instructions signal that EVZIO has delivered the intended dose of naloxone hydrochloride.
- EVZIO's red safety guard should not be replaced under any circumstances. However, the Trainer is designed for re-use and its red safety guard can be removed and replaced.
- It is recommended that patients and caregivers become familiar with the training device provided and read the *Instructions for Use*; however, untrained caregivers or family members should still attempt to use EVZIO during a suspected opioid overdose while awaiting definitive emergency medical care.
- Periodically visually inspect the naloxone solution through the viewing window. If the solution is discolored, cloudy, or contains solid particles, replace it with a new EVZIO.
- Replace EVZIO before its expiration date.

VII. Outstanding Deficiencies

N/A – Recommend Approval of Supplement with PMR listed in Section VIII.

VIII. Post-Market Commitments / Post-Market Requirements

The consulting reviewer proposes the following language for Post-Market Requirements related to combination product reliability.

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:
 - a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as $R(t) = x\%$, where t = time and $x\%$ = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning (as described below). The reliability requirements should be verified with a high degree of statistical confidence.
 - b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
 - c. Describe the use conditions for the product.
 - d. Define functionality required for reliability.
 - e. Define failure, as it relates to assessing the reliability requirements.

- f. Provide data to verify the reliability requirements. The acceptable endpoints (i.e. acceptance criteria) for this data should be linked to your definition of failure above.
 - g. Devices assessed within the reliability verification should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.
 - i. Shipping
 - ii. Aging
 - iii. Storage orientation and conditions
 - iv. Vibration handling
 - v. Shock handling (e.g., resistance to random impacts, such as being dropped).
 - h. Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.
 - i. Activation orientation
 - ii. Environmental temperature
 - i. Describe how manufacturing controls have been adequately implemented to achieve the reliability specification in the release product lots.
2. Establish a post-market monitoring program for detection and evaluation of under-dose and failure-to-dose events, regardless of cause, and provide periodic reports to the Agency which contains descriptions of each reported event along with results of root-cause and contributing-cause analyses.

IX. Recommendation

Device Constituent Parts of Combination Product Approvable for 2 mg dose with (2) Post-Marketing Requirements for device reliability – Please see Section VIII for draft PMR language.

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/s/

DIANA L WALKER

10/14/2016

Placed in DARRTS for CDRH reviewers John McMichael and Branch Chief Alan Stevens

Product Quality Microbiology Review

06 Sept 2016

NDA: 205787/S-007

Drug Product Name

Proprietary: Evzio

Non-proprietary: naloxone hydrochloride injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
04/19/2016	04/19/2016	N/A	06/10/2016
08/11/2016	08/11/2016	N/A	N/A
08/29/2016	08/29/2016	N/A	N/A

Applicant/Sponsor

Name: Kaleo, Inc.

Address: 111 Virginia St.
Suite 300
Richmond, VA 23219

Representative: Glen Kelley

Telephone: (804) 545-6368

Email: glen.kelley@kaleopharma.com

Name of Reviewer: Daniel J. Schu, Ph.D.

Conclusion: This submission **is recommended** for approval on the basis of product quality microbiology.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Prior Approval CMC Supplement
 2. **SUBMISSION PROVIDES FOR:** The submission provides for a new 2.0 mg (5 mg/mL) strength Naloxone Auto-Injector (NAI, 2.0 mg or NAI-HD).
 3. **MANUFACTURING SITE:**
 (b) (4)
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Single use autoinjector with voice prompts
 - 0.4 mg (0.4 mg/0.4 mL); 2.0 mg (2.0 mg/0.4 mL) sterile, non-preserved naloxone in a glass cartridge
 - Intramuscular or subcutaneous injection
 5. **METHOD(S) OF STERILIZATION:**  (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Treatment of opioid-induced respiratory depression.
- B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology Review of NDA 205787 (N205787R1.doc), dated 07 March 2014, and deemed adequate.
- C. **REMARKS:** The submission was provided in the eCTD format. A 06 May 2016 request was submitted requesting priority review designation. The application was granted priority review designation on 09 June 2016.

A microbiology information request was forwarded to the applicant by the Senior Regulatory Project Manager on 22 July 2016. The applicant requested a T-con with the Microbiology Review Team for further clarification on the 22 July 2016 information request. A T-con between the Regulatory Project Manager, Microbiology Review Team and the applicant occurred on 27 July 2016, in which clarification was provided by the Microbiology Review Team. During the T-con, the applicant agreed to the recommendations, and to amend the application within the requested 30 day period. It was noted that additional time would be required for a bacterial retention study with the new formulation of the drug product with the approved  (b) (4).

The applicant amended the application with responses to this information request on 11 August 2016. As noted in the 27 July 2016 T-con, the bacterial retention study was not provided with the responses. The response stated the study would be provided by August 29-September 2. The applicant amended the application with the bacterial retention study on 29 August 2016. Applicant responses are summarized and reviewed in appropriate sections of this review.

filename: N205787S007MR01.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – NDA 205787/S-007 is **recommended** for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A.

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This is a combination drug/device product. (b) (4)

[Redacted]

- B. **Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. **Contains Potential Precedent Decision(s)**- Yes No

- III. **Product Quality Microbiology Risk Assessment**- The proposed change to the manufacturing process poses no additional risk to the microbiology quality of the subject drug product.

IV. Administrative

- A. **Reviewer's Signature** _____
Daniel J. Schu, Ph.D.
- B. **Endorsement Block** _____
Stephen E. Langille, Ph.D.
Team Leader
- C. **CC Block**
Panorama

Daniel J. Schu -A
(Affiliate)

Digitally signed by Daniel J. Schu -A (Affiliate)
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH,
ou=People, 0.9.2342.19200300.100.1.1=0014362959,
cn=Daniel J. Schu -A (Affiliate)
Date: 2016.09.06 08:36:00 -04'00'

Stephen E.
Langille -S

Digitally signed by Stephen E. Langille -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300151320,
cn=Stephen E. Langille -S
Date: 2016.09.06 08:40:38 -04'00'

BIOPHARMACEUTICS REVIEW			
Office of New Drug Products			
Application No.:	NDA 205787 S017		Primary Reviewer: Vincent (Peng) Duan, Ph.D. Acting Quality Assessment Lead: Haritha Mandula, Ph.D.
Submission Date:	03/29/2016		
Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)		Acting Branch Chief: Tapash Ghosh, Ph.D.
Applicant:	Kaleo Pharma		
Trade Name:	EVZIO	Date Assigned:	04/27/2016
Generic Name:	Naloxone HCl injection	Date of Review:	07/01/2016
Indication:	<ul style="list-style-type: none"> • Treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression • Intended for immediate administration as emergency therapy in settings where opioids may be present. • Not a substitute for emergency medical care. 		Type of Submission: NDA Supplement (Addition of new strength)
Formulation/strengths:	Parenteral formulation in auto-injector, 0.4 mg and 2.0 mg naloxone HCl		
Route of Administration:	intramuscular (IM) or subcutaneous (SC)		

Review Assessment:

Background:

NDA 205787, Naloxone HCl (NAI) 0.4 mg/0.4 mL, was approved on April 3, 2014, for the treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. In this supplement, the Applicant seeks the approval of a higher strength 2.0 mg NAI (5 mg/mL, 0.4 mL) Naloxone HCl auto injector. Table 1 shows the NAI drug composition for different strengths (Table 1).

Table 1. Composition of the proposed drug product

Component	Function	0.4 mg NAI Amount	2.0 mg NAI Amount
Naloxone HCl, Anhydrous ¹	Active	1 mg/mL	5 mg/mL
Sodium Chloride	(b) (4)		
Hydrochloric Acid			
Water for Injection			

(b) (4)

(b) (4)

(b) (4)

The Applicant evaluated the impact of the increase in naloxone HCl concentration from 1 mg/mL to 5 mg/mL, and reached the following conclusions:

- The naloxone HCl was readily soluble at 5 mg/mL.
- The pH was adequately adjusted to 3.4.
- The osmolality was within specification ((b) (4) mOsm) without altering the sodium chloride concentration.
- The density of the 5 mg/mL solution was slightly greater than the 1 mg/mL solution, (b) (4) versus (b) (4) g/mL, respectively.
- The viscosities of the 5 mg/mL solution and the 1 mg/mL solution at 20 °C were (b) (4) mPa*s, respectively, indicating a viscosity (b) (4)

(b) (4)

;

The proposed 2.0 mg NAI is a parenteral formulation in auto-injector administrated by IM or SC similar to the approved 0.4 mg NAI. The only difference between these two formulations is the concentration of naloxone HCl (1 mg/mL vs. 5 mg/mL). As shown in Table 2A and Table 2B, the two strengths have the same specifications in pH and osmolality. The batch analysis data shown in Table 5 for 2.0 mg NAI met the specifications in pH and osmolality.

Table 2A. Quality Control Specifications for NAI, 0.4 mg

Test	Analytical Procedure	Acceptance Criterion	NAI Release	Drug Constituent Component and NAI Stability/Shelf Life
Appearance	Visual	Clear, colorless solution in a glass cartridge with a gray plunger and crimp cap.	X ^a	X
pH	USP	(b) (4)	X ^a	X
Osmolality	USP	(b) (4) mOsm/kg	X ^c	
Identification	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	Matches reference standard retention time.	X ^a	
Assay	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) % LC	X ^a	
		(b) (4) % LC		X
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) NMT (b) (4) %	X ^a	
		Single Unspecified: NMT % Total Impurities: NMT %		

Test	Analytical Procedure	Acceptance Criterion	NAI Release	Drug Constituent Component and NAI Stability/Shelf Life
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % Single Unspecified: NMT (b) (4) % Total Impurities: NMT (b) (4) %		X
Particulate Matter	USP	NMT (b) (4) µm and NMT (b) (4) µm per container	X ^c	X
Sterility	USP	Conforms	X ^d	X
Endotoxin	USP	NMT (b) (4) EU/mg of Naloxone HCl	X ^d	X
Activation Force		(b) (4) lbs	X ^b	
Volume Dispensed		(b) (4) mL	X ^b	X ^b
Dispensing Time	Section 3.2.D.2.11	NMT (b) (4) seconds	X ^b	X ^b
Exposed Needle Length		(b) (4) in	X ^b	X ^b

^a Results taken from testing conducted on the Drug Cartridge Assembly.

^b Device Performance Specification: Not applicable to Drug Constituent Component.

^c Results taken from Drug Constituent Component release testing at (b) (4) (Section 3.2.P.3.4).

^d Test performed on NAI finished product.

Table 2B. Quality Control Specifications for NAI, 2.0 mg

Test	Analytical Procedure	Acceptance Criterion	NAI Release	Drug Constituent Component and NAI Stability/Shelf Life
Appearance	Visual	Clear, colorless solution in a glass cartridge with a gray plunger and crimp cap.	X ^a	X
pH	USP	(b) (4)	X ^a	X
Osmolality	USP	(b) (4) mOsm/kg	X ^c	
Identification	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	Matches reference standard retention time.	X ^a	
Assay	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) % LC	X ^a	
		(b) (4) % LC		X
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % Single Unspecified: NMT (b) (4) % Total Impurities: NMT (b) (4) %	X ^a	

Test	Analytical Procedure	Acceptance Criterion	NAI Release	Drug Constituent Component and NAI Stability/Shelf Life
Related Substances	Section 3.2.P.5.2.1 (ATM-8v3 or IN025-ATM-001)	(b) (4) NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % NMT (b) (4) % Single Unspecified: NMT (b) (4) % Total Impurities: NMT (b) (4) %		X
Particulate Matter	USP	NMT (b) (4) µm and NMT (b) (4) µm per container	X ^c	X
Sterility	USP	Conforms	X ^d	X
Endotoxin	USP	NMT (b) (4) EU/mg of Naloxone HCl	X ^d	X
Activation Force	Section 3.2.D.2.11	(b) (4) lbs	X ^b	
		(b) (4) lbs		X ^b
Volume Dispensed		(b) (4) mL	X ^b	X ^b
Dispensing Time		NMT (b) (4) seconds	X ^b	X ^b
Exposed Needle Length		(b) (4) in	X ^b	X ^b

^a Results taken from testing conducted on the Drug Cartridge Assembly.
^b Device Performance Specification: Not applicable to Drug Constituent Component.
^c Results taken from Drug Constituent Component release testing at (b) (4) (Section 3.2.P.3.4).
^d Test performed on NAI finished product.

Furthermore, as the Applicant evaluated, the increase in naloxone HCl concentration in the 2.0 mg NAI will not significantly affect either the solubility of the drug substance, or the density and the viscosity of the solution.

For the approved 0.4 mg strength, the naloxone HCl bioavailability has been measured in clinical bioavailability study IJ-900DV-O30, and was bioequivalent to a naloxone HCl USP injection reference listed drug.

The Applicant also conducted clinical study KA-900DV-O5A to demonstrate the dose proportionality of the approved 0.4 mg strength NAI to the proposed 2.0 mg strength NAI.

Study KA-900DV-O5A is a randomized, single-dose, three-period crossover bioavailability, dose proportionality PK, safety and tolerability study, was conducted in healthy human subjects. The objectives of this study were:

- To evaluate the dose proportionality of 0.4 mg and 2.0 mg naloxone HCl following IM or SC injection using an NAI,
- To characterize the PK profiles of 0.4 mg, 0.8 mg (two 0.4 mg injections), and 2.0 mg naloxone HCl following IM or SC injection using NAIs, and
- To assess the safety and tolerability of 0.4 mg, 0.8 mg (two 0.4 mg injections), and 2.0 mg naloxone HCl injection using NAIs.

Figure 1 shows plasma concentration time data from study KA-900DV-05A. Table 3 shows the summary of naloxone plasma pharmacokinetic parameters and dose proportionality results from study KA-900DV-05A. Based on power model C_{max} and AUC of naloxone HCl are dose proportional over the dose range (0.4 mg to 2.0 mg NAI). Similarly, dose proportionality comparison of 2.0 mg and 0.4 mg NAIs or 0.4 mg NAIs and 0.8 mg NAIs, concluded that AUC parameters are dose proportional. As stated in meeting minutes dated December 23, 2014, the Agency is mainly interested in the PK profile for the 2 mg dose and how the product will perform. Dose proportionality outside of the 80 – 125 range will not necessarily preclude approval. Therefore, the slight off dose proportional for C_{max} was not a concern as stated by the Clinical Pharmacology Reviewer. The final acceptance of this clinical study will be determined by the Office of Clinical Pharmacology. Please refer to clinical pharmacology review for additional details.

Table 3. Summary of Naloxone Plasma Pharmacokinetic Parameters and Dose Proportionality Results (Study KA-900DV-05A)

Treatment	Statistic	C_{max} (pg/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC ₀₋₁ (pg.h/mL)	AUC _{0-inf} (pg.h/mL)
Pharmacokinetic Parameters						
Reference (0.4 mg NAI)*	Mean (SD)	1328 (836)		1.58 (0.457)	1817 (290)	1995 (326)
	%CV	62.9		28.9	16.0	16.3
	Median (Min-Max)	980 (503-4220)	0.25 (0.09-0.84)	1.47 (1.05-2.76)	1864 (1322-2269)	1991 (1427-2688)
Test (0.8 mg naloxone HCl [two 0.4 mg NAIs])*	Mean (SD)	2156 (1021)		1.52 (0.360)	3498 (691)	3776 (720)
	%CV	47.4		23.7	19.8	19.1
	Median (Min-Max)	1855 (913-4160)	0.21 (0.09-0.85)	1.40 (1.11-2.39)	3435 (2334-5186)	3776 (2584-5438)
Test (2.0 mg NAI)	Mean (SD)	7905 (3617)		1.53 (0.382)	9657 (1488)	10330 (1565)
	%CV	45.8		25.0	15.4	15.2
	Median (Min-Max)	6950 (3020-14900)	0.25 (0.13-0.67)	1.47 (0.90-2.31)	9703 (6896-12760)	10410 (7420-13150)
Statistical Assessments of Dose Proportionality						
Dose normalized 2.0 mg / 0.4 mg†	GMR	1.24			1.06	1.05
	90% CI for ratio	1.04, 1.49			1.02, 1.11	1.01, 1.09
Dose normalized 0.8 mg / 0.4 mg	GMR	0.85			0.96	0.94
	90% CI for ratio	0.71, 1.02			0.92, 1.00	0.91, 0.98
Power Model (linear regression)	Slope	1.15			1.04	1.03
	95% CI	0.97, 1.33			0.98, 1.11	0.97, 1.09

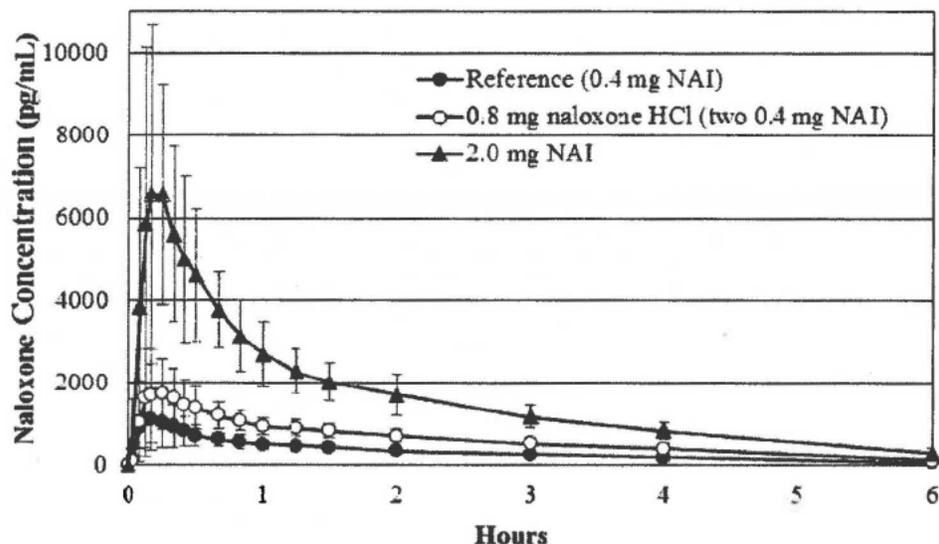
Sources: KA-900DV-05A Clinical Study Report Tables 14.2.2.1, 14.2.3.1, 14.2.3.2 and 14.2.3.3

CI = confidence interval; GMR = geometric mean ratio; Min = minimum; Max = maximum; %CV = percentage coefficient of variation; SD = standard deviation

*N=23 for AUC_{0-inf} and $T_{1/2}$ due to R^2 adjusted less than 0.90; therefore λ_z could not be calculated for 1 subject in 0.4 mg NAI and 0.8 mg naloxone HCl treatment groups.

†Comparison of 2.0 mg and 0.4 mg NAI was the primary comparison for dose proportionality; comparison of 0.4 mg NAI and 0.8 mg naloxone HCl (two 0.4 mg NAIs) and power model approach were secondary.

Figure 1. Mean (\pm SD) Naloxone Plasma Concentration-Time Data (Study KA 900DV-05A)



Source: KA-900DV-05A Clinical Study Report Figure 14.2.3

Overall, the proposed 2.0 mg strength NAI is a parental formulation for IM or SC administration, without change in delivery mechanism. The only difference in formulations between 2.0 mg strength and the approved 0.4 mg strength is the different concentration of API, and they have the same specifications in pH and osmolality. The device constituent component of the auto injector has been tested by the volume dispensed test, which confirmed the dose accuracy as a result of NAI injection (0.340-0.460 mL for both NAI strengths resulting in a nominal dose of 0.4 mg or 2.0 mg naloxone HCl). A BA/BE study has been conducted for 0.4 mg strength NAI to show bioequivalence to the listed drug product. Naloxone HCl also shows dose proportionality over the dose range of 0.4 mg to 2.0 mg in clinical study KA 900DV-05A. Therefore, based on the 21 CFR 320.24(b) (6) regulation, from Biopharmaceutics perspective, the bridge (bioavailability/bioequivalence) between the proposed drug product and the listed drug product has been established.

Evaluation of manufacturing site change

2.0 mg NAI was developed at (b) (4). One technical batch (Batch D01087) and three process qualification batches (PQ Batches D01160, D01161, and D01162 placed in stability test) were manufactured in (b) (4). Then the process was transferred to (b) (4) for the manufacturing of a technical batch and a confirmation batch (Table 4). Batch D01162A is a clinical batch used in clinical study KA-900DV-05A. Table 5 shows the batch release analysis for these batches manufactured at different sites, and they all confirmed the proposed drug product specifications (e.g. pH and osmolality). The batches from different manufacturing sites are comparable.

Table 4. Disposition of Filled Cartridges

Manufacturer	Drug Constituent Component Batch Number	Cartridges Filled	Date of Manufacture ^a	Use
(b) (4)	R256p3	(b) (4)	May 29, 2014	Stability
	D01087		December 5, 2014	Stability
	D01160		March 16, 2015	Registration stability
	D01161		March 18, 2015	Registration stability
	D01162		March 30, 2015	Registration stability, device build
			January 18, 2016	Demonstration of commercial mixing and filling accuracy
			February 1, 2016	Stability

^a The date when (b) (4)

Table 5. Batch Release Analysis for 2.0 mg Strength of Drug Constituent Component of NAI

Test	Acceptance Criterion	R256p3	D01087 ^a	D01160A	D01161A	D01162A
Appearance	Clear, colorless solution in a glass cartridge with a gray plunger and crimp cap.	Conforms	B.M.E. Conforms	Conforms	Conforms	Conforms
pH	(b) (4)	(b) (4)				
Osmolality	(b) (4) mOsm/kg	(b) (4)				
Identification	Matches reference standard retention time	Conforms	B.M.E. Conforms	Conforms	Conforms	Conforms
Assay	(b) (4) % LC	(b) (4)				
Related Substances (b) (4)	NMT (b) (4) %	(b) (4)				
	NMT %	(b) (4)				
	NMT %	(b) (4)				
Single, Unspecified ^b	NMT %	(b) (4)				
Total Impurities	NMT %	(b) (4)				
Break loose and Glide Forces	Max. Break force NMT	(b) (4)				
	Max. Glide force NMT	(b) (4)				
	Mean Glide force NMT	(b) (4)				
Particulate Matter	NMT (b) (4) ≥ 10 µm and NMT (b) (4) ≥ 5 µm and per container	(b) (4)				
Sterility	(b) Conforms	(b) (4)				
Endotoxin	NMT (4) EU/mg of Naloxone HCl	(b) (4)				

Refer to Table 3.2.P.3.4-3 for Acceptance Criteria.

^a Tested beyond 30 days after manufacture so stability limits applied, instead of release limits (notably pH).

B - Beginning of batch; M - Middle of batch; E - End of batch

LC - Label claim; LOQ - Limit of quantitation

ND - Not detected; NS - Not scheduled

Table 5. Batch Release Analysis for 2.0 mg strength of Drug Constituent Component of NAI (continued)

Test	Acceptance Criterion	(b) (4) Technical Batch (INPA01)	(b) (4) Confirmation Batch (INPB02)
Appearance	Clear, colorless solution in a glass cartridge with a gray plunger and crimp cap.	Conforms	Conforms
pH	(b) (4)		(b) (4)
Osmolality	(b) (4) mOsm/kg		
Identification	Matches reference standard retention time.	Conforms	Conforms
Assay	(b) (4) % LC		(b) (4)
Related Substances	(b) (4) NMT (b) (4) %		
	(b) (4) NMT %		
	(b) (4) NMT %		
Single, Unspecified °	(b) (4) NMT %		
Total Impurities	(b) (4) NMT %		
Break loose and Glide Forces	Max. Break force NMT (b) (4) N		
	Max. Glide force NMT N		
	Mean Glide force NMT N		
Particulate Matter	(b) (4) NMT (b) (4) 10 µm and (b) (4) µm and per container		
Sterility	(b) (4) Conforms		
Endotoxin	(b) (4) NMT (4) EU/mg of Naloxone HCl		

Refer to Table 3.2.P.3.4-3 for Acceptance Criteria

- LC - Label claim
- LOQ - Limit of quantitation
- ND - Not detected
- NS - Not scheduled

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/s/

JONATHAN T DOW
10/28/2016