

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205787Orig1s000**

**CHEMISTRY REVIEW(S)**

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

<b>Application:</b>	NDA 205787/000	<b>Action Goal:</b>	
<b>Comp Date:</b>	20-DEC-2013	<b>District Goal:</b>	21-APR-2014
<b>Regulatory:</b>	20-JUN-2014		
<b>Applicant:</b>	KALEO INC 111 VIRGINIA ST STE 405 RICHMOND, VA 23219	<b>Brand Name:</b>	0.4 MG NALOXONE AUTO-INJECTOR (NALOXONE)
		<b>Estab. Name:</b>	
<b>Priority:</b>	34	<b>Generic Name:</b>	0.4 MG NALOXONE AUTO-INJECTOR (NALOXONE)
<b>Org. Code:</b>	170	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; INJECTION; NALOXONE HYDROCHLORIDE; .4MG

**Application Comment:**

<b>FDA Contacts:</b>	Y. WANG	Prod Qual Reviewer	3017961479
	J. COLE	Micro Reviewer	3017965148
	L. RIVERA	Product Quality PM	3017964013
	D. WALKER	Regulatory Project Mgr	(HFD-170) 3017964029
	J. PINTO	Team Leader	3017961733

<b>Overall Recommendation:</b>	ACCEPTABLE	on 02-APR-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 16-JAN-2014	by EES_PROD		
	PENDING	on 10-JAN-2014	by EES_PROD		
	PENDING	on 10-JAN-2014	by EES_PROD		

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** **CFN:** **FEI:** (b) (4)  
 (b) (4)

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

**Establishment Comment:** FINAL PRODUCT DRUG QUALITY CONTROL TESTING (STABILITY SAMPLES STORAGE, QUALITY CONTROL RELEASE & STABILITY TESTING, DEVICE PERFORMANCE STABILITY TESTING) (on (b) (6) by L. RIVERA () 3017964013)

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	10-JAN-2014				RIVERAL
SUBMITTED TO DO INITIAL "AC"	18-JAN-2014	10-Day Letter			WILLIAMSJU
DO RECOMMENDATION	24-JAN-2014			ACCEPTABLE	WALTERSJ

THERE HAS BEEN ONE INITIAL INSPECTION CONDUCTED AT THIS FIRM.  
 THE MOST RECENT COMPREHENSIVE INSPECTION OF THE FIRM WAS CONDUCTED FROM (b) (6) SYSTEMS COVERED DURING THIS INSPECTION INCLUDED QUALITY, FACILITIES AND EQUIPMENT, AND LABORATORY. NO FDA-483 WAS ISSUED TO FIRM MANAGEMENT AT THE CONCLUSION OF THE INSPECTION. THE PROFILE CLASS CTL WAS FOUND ACCEPTABLE. THE INSPECTION WAS CLASSIFIED NO ACTION INDICATED (NAI). HOWEVER, DISCUSSION ITEMS ADDRESSED WITH FIRM MANAGEMENT ARE DESCRIBED BELOW:

(b) (4)

BASED UPON FILE REVIEW, THE DISTRICT RECOMMENDS APPROVAL OF THE FIRM FOR ITS LISTED RESPONSIBILITIES IN THE APPLICATION.

OC RECOMMENDATION	30-JAN-2014			ACCEPTABLE	CAPACCIDANIC
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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment:

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	16-JAN-2014				RIVALAL
SUBMITTED TO DO CONFIRMATION FROM NDMAB, THAT THE COVERAGE UNDER THE THIS FIRM	21-JAN-2014	10-Day Letter			SHARPT
DO RECOMMENDATION	21-JAN-2014			ACCEPTABLE	MSPATARO
RECOMMENDATION	30-JAN-2014			ACCEPTABLE	CAPACCIDANIC



**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)  
 (b) (4)  
 DMF No: AADA:  
 Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE RELEASE TESTER  
 Establishment Comment: DS MANUFACTURING & QUALITY CONTROL (on (b) (6) by L. RIVERA () 3017964013)  
 Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	10-JAN-2014				RIVERAL
OC RECOMMENDATION	16-JAN-2014			ACCEPTABLE	WILLIAMSJU

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: FINAL DEVICE ASSEMBLY (on [REDACTED] (b) (6) by L. RIVERA () 3017964013)

Profile: DEVICE KIT ASSEMBLER OAI Status: NONE  
STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
<u>OAI Submit To OC</u>					
<u>Request to Extend Re-eval Date To</u>					
<u>Extension Request Comment</u>					
<u>Reason</u>					

SUBMITTED TO OC	16-JAN-2014				RIVERAL
SUBMITTED TO DO	17-JAN-2014	GMP Inspection			WILLIAMSJU
THE DEVICE PORTION DOES NOT REQUIRE A PRODUCT SPECIFIC INSPECTION, ONLY DRUG. CDRH CAN PROVIDE SOME APPROPRIATE GUIDANCE FOR THE DEVICE ASPECT OF THE INSPECTION					
ASSIGNED INSPECTION TO IB	27-JAN-2014	GMP Inspection			DEMERSON
INSPECTION PERFORMED	[REDACTED] (b) (6)		[REDACTED] (b) (6)		DEMERSON
THE FIRM IS NOT YET READY TO MANUFACTURE THE DEVICE FOR THIS DRUG/DEVICE PRODUCT. THE FIRM HAS NOT STARTED VALIDATION FOR THE DEVICE AND THE CLEAN ROOM IN WHICH THE DEVICE IS ASSEMBLED IS NOT QUALIFIED.					
INSPECTION SCHEDULED	02-APR-2014		[REDACTED] (b) (6)		DEMERSON
DO RECOMMENDATION	02-APR-2014			WITHHOLD	DEMERSON
THE FIRM IS NOT YET READY TO MANUFACTURE THE DEVICE FOR THIS DRUG/DEVICE PRODUCT. THE FIRM HAS NOT STARTED VALIDATION FOR THE DEVICE AND THE CLEAN ROOM IN WHICH THE DEVICE IS ASSEMBLED IS NOT QUALIFIED. THE DISTRICT RECOMMENDS WITHHOLD FOR THIS SITE FOR THIS APPLICATION AT THIS TIME.					
OC RECOMMENDATION	02-APR-2014			ACCEPTABLE	WILLIAMSJU
CDRH/OC HAS DETERMINED THIS SITE IS ACCEPTABLE TO SUPPORT THIS APPLICATION, THE BASIS OF WHICH IS DESCRIBED IN THEIR POST-INSPECTION REVIEW MEMO ICC1400187, DATED APRIL 1, 2014, IN DARRTS.					

SUBMITTED TO OC	16-JAN-2014				RIVERAL
SUBMITTED TO DO	17-JAN-2014	Product Specific and GMP Inspection			WILLIAMSJU
THIS FIRM WILL BE REGULATED UNDER 211 AND 820 FOR THIS PRODUCT. THE FIRM DOES HAVE EXPERIENCE WITH 820 BUT HAS NEVER MANUFACTURED A FINISHED DOSAGE FORM UNDER 211. REQUESTING A DRUG SPECIALIST CONDUCT THE INSPECTION; CDRH CAN ADEQUATELY GUIDE THE INVESTIGATOR REGARDING 820.					
ASSIGNED INSPECTION TO IB	28-JAN-2014	Product Specific and GMP Inspection			DEMERSON

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

INSPECTION PERFORMED (b) (6) (b) (6) DEMERSON  
THE INSPECTION CONDUCTED FOR DRUGS SHOWS THAT THE FIRM RECEIVED THE FINAL DRUG PRODUCT IN ITS CONTAINER WHICH THEY THEN ADD TO THE DEVICE KIT FOR SELF INJECTION. THERE WERE NO SIGNIFICANT GMPs IDENTIFIED FOR THE DRUG COMPONENT.

INSPECTION SCHEDULED 02-APR-2014 (b) (6) DEMERSON

DO RECOMMENDATION 02-APR-2014 ACCEPTABLE DEMERSON  
THERE WERE NO SIGNIFICANT ISSUES RELATIVE TO THE DRUG PRODUCT DURING THE INSPECTION. THE DISTRICT RECOMMENDS APPROVAL FOR THIS SITE FOR THIS APPLICATION FOR THE DRUG PRODUCT.

OC RECOMMENDATION 02-APR-2014 ACCEPTABLE WILLIAMSJU

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)  
(b) (4)

DMF No: AADA:

Responsibilities: INTERMEDIATE OTHER TESTER

Establishment Comment: DRUG CONSTITUENT COMPONENT VISUAL INSPECTION (on (b) (6) by L. RIVERA () 3017964013)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
<u>OAI Submit To OC</u>					
<u>Request to Extend Re-eval Date To</u>					
<u>Extension Request Comment</u>					
<u>Reason</u>					

SUBMITTED TO OC	10-JAN-2014				RIVERAL
OC RECOMMENDATION	16-JAN-2014			ACCEPTABLE	WILLIAMSJU

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: (b) (4)

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
<u>OAI Submit To OC</u>					
<u>Request to Extend Re-eval Date To</u>					
<u>Extension Request Comment</u>					
<u>Reason</u>					

SUBMITTED TO OC	10-JAN-2014				RIVERAL
SUBMITTED TO DO	15-JAN-2014	10-Day Letter			WILLIAMSJU
DO RECOMMENDATION	16-JAN-2014			ACCEPTABLE	MROSE
RECOMMENDATION	17-JAN-2014			ACCEPTABLE	SHARPT

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)  
 (b) (4)

DMF No: AADA:

Responsibilities: INTERMEDIATE OTHER TESTER

Establishment Comment: DRUG CONSTITUENT COMPONENT VISUAL INSPECTION AND QUALITY CONTROL TESTING, STERILITY, ENDOTOXIN, OSMOLALITY, PARTICULATE MATTER, HPLC (ASSAY AND RELATED SUBSTANCES) (on (b) (6) by L. RIVERA ( ) 3017964013)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	10-JAN-2014				RIVERAL
OC RECOMMENDATION	10-JAN-2014			ACCEPTABLE	WILSONT

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: FEI: (b) (4)  
(b) (4)

DMF No: AADA:

Responsibilities: INTERMEDIATE OTHER TESTER

Establishment Comment: DRUG CONSTITUENT COMPONENT VISUAL INSPECTION AND QUALITY CONTROL TESTING. STERILITY  
ENDOTOXIN, OSMALITY, PARTICULATE MATTER, AND HPLC (ASSAY AND RELATED SUBSTANCES) (on (b) (6)  
by L. RIVERA () 3017964013)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
<u>OAI Submit To OC</u>					
<u>Request to Extend Re-eval Date To</u>					
<u>Extension Request Comment</u>					
<u>Reason</u>					

SUBMITTED TO OC	10-JAN-2014				RIVERAL
OC RECOMMENDATION	16-JAN-2014			ACCEPTABLE	WILLIAMSJU

# **NDA 205787**

## **EVZIO (Naloxone Hydrochloride) Auto-Injector**

**Kaleo, Inc (Formally Intelliject, Inc.)**

**Ying Wang, PhD**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division III, Branch VIII**

**CMC REVIEW OF NDA 205787  
For the Division of Anesthesia, Analgesia and Addition Product**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 205787
2. REVIEW #: 1
3. REVIEW DATE: March 14, 2014
4. REVIEWER: Ying Wang, PhD
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	12/20/2013
Correspondence (C)	
Amendment (BC)	2/11/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Kaleo, Inc (Formally Intelliject, Inc.)  
Address: 111 Virginia St, Suite 405, Richmond, VA 23219  
Representative: Ronald D. Gunn  
Telephone: 804-545-6376

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: EVZIO Auto-Injector
- b) Non-Proprietary Name: Naloxone Hydrochloride Auto-Injector
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5
  - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOLOGY CATEGORY: Opioid Antagonist

11. DOSAGE FORM: Auto-Injector

## CMC Review Data Sheet

12. STRENGTH/POTENCY: 0.4 mg
13. ROUTE OF ADMINISTRATION: IM or SC
14. Rx/OTC DISPENSED:  Rx  OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)  
 SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Generic Name**

Naloxone Hydrochloride Dihydrate

**Compendial Name (USP)**

Naloxone Hydrochloride, USP

**USAN Name**

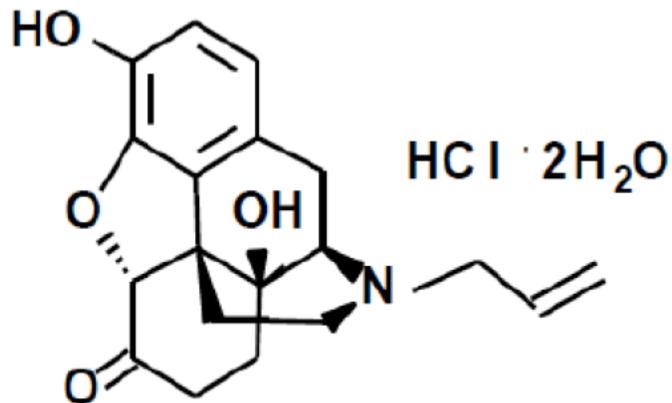
Naloxone Hydrochloride

**Chemical Name(s)**

17-Allyl-4,5 $\alpha$ -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate  
Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5 $\alpha$ )-, dihydrate

**Structure**

## CMC Review Data Sheet

**Molecular Formula**C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub>·HCl·2H<sub>2</sub>O**Relative Molecular Mass**

(b) (4)

CMC Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/22/2013	Reviewed by Arthur Shaw
	III			1	Adequate	12/15/2008	Reviewed by Steven Donald from microbiology
	III			4	N/A		See (b) (4) review in NDA
	III			4	N/A		See (b) (4) review in NDA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: N/A**

CMC Review Data Sheet

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Approval	3/20/2014	Carlic Huynh
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	See review comments	2/4/2014	Vicky Borders-Hemphill
EA	Categorical exclusion acceptable (see this review)		Ying Wang
Microbiology	Approval	3/7/2014	Jessica G. Cole

## Executive Summary Section

# The CMC Review for NDA 205787

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA is recommended for APPROVAL from the chemistry, manufacturing, and control (CMC) perspective pending overall ACCEPTABLE recommendation from the Office of Compliance (OC). Please note all facilities associated with this NDA have been deemed acceptable by OC except one of the device assembling facilities (b) (4). The inspection for this facility is still on-going as of this writing.

EVZIO Auto-Injector is stored at controlled room temperature 15°C to 25°C (59°F to 77°F) excursions permitted between 4°C and 40°C (between 39°F and 104°F). Expiry of earlier of 27 months from the manufacturing date for the Drug Constituent Component (b) (4) or 24 months from the date of final assembly, packaging and labeling is proposed and granted.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

Drug substance naloxone hydrochloride is a white to off-white powder. It is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol, practically insoluble in ether and in chloroform. Drug substance information is referenced in DMF (b) (4) for which (b) (4) is the holder. Specification which is provided in the NDA for the drug substance mostly follow USP and EP monographs. Additional specifications for related substance meet ICH Q3A guideline. Drug substance has retest period of (b) (4) months.

##### (2) Drug Product

## Executive Summary Section

EVZIO auto-injector is a single use auto-injector that delivers 0.4 mg naloxone hydrochloride via subcutaneous or intramuscular injection. EVZIO is a drug-device combination product containing a prefilled naloxone HCl drug constituent component.

The Drug Constituent Component of EVZIO is a parenteral solution formulation that is (b) (4) filled into a Type I (b) (4) glass cartridge and enclosed by an (b) (4) plunger and (b) (4) lined crimp cap (i.e., primary container closure). The parenteral formulation is (b) (4) listed drug product (International Medicinal Systems, Naloxone HCl Injection, USP [1mg/mL] Luer-Jet™ Prefilled Syringe 2 mg / 2mL).

The Device Constituent Component of EVZIO is a (b) (4), needle-based system that delivers the prescribed dose of naloxone HCl into the user. When activated, EVZIO will inject a single dose of 0.4 mL (0.4 mg of naloxone HCl). EVZIO is designed to be a single use device, so any residual parenteral formulation remaining in the device after injection of the dose cannot be utilized. The Device Constituent Component of EVZIO is reviewed by CDRH and is found acceptable.

From risk perspective, ensuring sterility of the drug product during manufacturing and packaging process is critical for the safety of the drug. This aspect of the drug product is reviewed by microbiology reviewer and is found acceptable. Drug product is stable during stability and has relatively low impurity level. Stability data for 12 month long term storage condition (25°C/60% RH), 6 month intermediate storage condition (30°C/65% RH) and 6 month accelerated storage condition (40°C/75% RH) are provided in the submission. The stability data support the proposed expiry of earlier of 27 months from the manufacturing date for the drug constituent component of EVZIO and 24 months from the date of final assembly, packaging and labeling of EVZIO.

**B. Description of How the Drug Product is Intended to be Used**

(b) (4)

An initial dose of 0.4 mg of naloxone hydrochloride may be administered intramuscularly or subcutaneously in patients (b) (4). If the desired degree of counteraction and improvement in respiratory functions is not obtained, after 2 or 3 minutes, another EVZIO dose may be administered. (b) (4)

(b) (4)

**C. Basis for Approvability or Not-Approval Recommendation**

## Executive Summary Section

This NDA is a 505(b)(2) application. The drug constituent component [REDACTED] (b) (4) [REDACTED] list drug of naloxone HCl injection. The [REDACTED] (b) (4) manufacturing process for the drug constituent component is a critical aspect of the drug product quality and is considered acceptable by microbiology reviewer. The proposed acceptance criteria for the drug constituent component meet regulatory guidelines for similar dosage form products and are acceptable. The device constituent component is deemed adequate by CDRH reviewer.

**III. Administrative****A. Reviewer's Signature:**

*(See appended electronic signature page)*

Ying Wang, PhD

**B. Endorsement Block:**

*(See appended electronic signature page)*

Prasad Peri, PhD, Branch Chief, Branch VIII, ONDQA

**C. CC Block:** entered electronically in DFS

42 Page(s) has been Withheld in Full as b4 (CCI/TS)  
immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

YING WANG  
03/21/2014

PRASAD PERI  
03/21/2014  
I concur

# Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

## I. Review Cover Sheet

- 1. OMPQ Reviewer: Juandria Williams
- 2. NDA/BLA Number: 205787  
Submission Date: December 20, 2013  
21<sup>st</sup> C. Review Goal Date: Tentatively March 28, 2014  
PDUFA Goal Date: June 20, 2014

### 3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Evzio
Established or Non-Proprietary Name (USAN) and strength:	Naloxone Hydrochloride Injection, USP
Dosage Form:	Autoinjector

### 4. SUBMISSION PROPERTIES:

Review Priority :	Priority
Applicant Name:	Kaleo, Inc.
Responsible Organization (OND Division):	DAAAP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
For Pre-Marketing Applications

## II. Application Detail

1. INDICATION: For the maintenance treatment of opioid dependence
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 0.4 mg/0.4 mL
4. Rx/OTC DISPENSED:   xRx       OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		x		
2.	Breakthrough Therapy Designation		x		
3.	Orphan Drug Designation		x		
4.	Unapproved New Drug		x		
5.	Medically Necessary Determination		x		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		x		
7.	Rolling Submission	x			The sponsor was granted a Fast Track designation, as well as rolling review and Priority review status.
8.	Drug/device combination product with consult	x			Consults requests submitted to CDRH (ODE and OC) 12/26/2013
9.	Complex manufacturing		x		
10.	Other (e.g., expedited for an unlisted reason)		x		

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### III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

<b>A. COMPLETENESS OF FACILITY INFORMATION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	x		Form 356h supplement
12.	Do all sites indicate they are ready to be inspected (on 356h)?	x		Form 356h supplement
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	x		Form 356h supplement
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	x		Form 356h supplement
15.	Additional notes (non-filing issue)	x		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		x	
	3. Is this first application by the applicant?		x	

\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

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<b>B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
16.	Have any Comparability Protocols been requested?		x	

<b>IMA CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
17.	Does this application fit one of the EES Product Specific Categories?	x		The (b) (4) has only device component manufacturing history and no finished dosage history.
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	x		
	Have all EERs been updated with final PAI recommendation?	x		
19.	<b>From a CGMP/facilities perspective, is the application fileable?</b>  If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	x		

## V. Overall Conclusions and Recommendations

<b>Is the application fileable? Yes</b>
<b>Based on Section IV, is a KTM warranted for any PAI? No</b> <b>If yes, please identify the sites in the above chart.</b>
<b>Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? No</b>
Comments for 74 Day Letter
1. N/A
2.
3.

## REVIEW AND APPROVAL (DARRTS)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JUANDRIA WILLIAMS  
02/26/2014

MAHESH R RAMANADHAM  
02/28/2014