

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205787Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

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

Application Comment:

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

| | | | | | |
|--------------------------------|------------|----------------|----------------|----|------------|
| Overall Recommendation: | 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

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

| | | | | | |
|---------------------------------|-------------|---------------|--|--|------------|
| 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 |
|-------------------|-------------|--|------------|--|--------------|

**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

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

| | | | | | |
|--|-------------|---------------|---------|------------|--------------|
| SUBMITTED TO OC | 16-JAN-2014 | | | | RIVERAL |
| SUBMITTED TO DO CONFIRMATION FROM NDMAB, THAT THE COVERAGE UNDER THE THIS FIRM | 21-JAN-2014 | 10-Day Letter | (b) (4) | | SHARPT |
| DO RECOMMENDATION | 21-JAN-2014 | | | ACCEPTABLE | MSPATARO |
| RECOMMENDATION | 30-JAN-2014 | | | ACCEPTABLE | CAPACCIDANIC |

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: **CFN:** **FEI:** 3007135538
 KALEO, INC.
 111 VIRGINIA ST STE 300
 RICHMOND, VA 232194159

DMF No: **AADA:**

Responsibilities: INTERMEDIATE MANUFACTURER

Establishment Comment:

Profile: NOT ELSEWHERE CLASSIFIED

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 | 16-JAN-2014 | | | | RIVERAL |
| SUBMITTED TO DO | 03-FEB-2014 | Product Specific and GMP Inspection | | | WILLIAMSJU |
| THIS FIRM WILL MAINTAIN THE DESIGN HISTORY FILE, FINAL PRODUCT COA, AND APPROVAL FOR DISTRIBUTION. IT WILL ALSO BE RESPONSIBLE FOR ANNUAL PRODUCT REVIEW AND FIELD ALERTS. | | | | | |
| ASSIGNED INSPECTION TO IB | 04-FEB-2014 | Product Specific and GMP Inspection | | | BSEEMAN |
| THIS FIRM WILL BE RESPONSIBLE FOR THE DESIGN HISTORY FILE AND FINAL PRODUCT RELEASE (DESIGN HISTORY FILE MAINTENANCE, FINAL PRODUCT CERTIFICATE OF ANALYSIS AND APPROVAL FOR DISTRIBUTION, AND ANNUAL PRODUCT REVIEW AND FIELD ALERTS) FOR THE MARKETING OF EVZIO, A NALOXONE AUTO-INJECTOR. THE FIRM DOES NOT PHYSICALLY MANUFACTURE ANY OF THE DRUG PRODUCT OR FINISHED DOSAGE. THIS NDA WAS GRANTED EXPEDITED REVIEW SUCH THAT THE REVIEW DIVISION IS PUSHING FOR SIGNATURE AUTHORITY REVIEW TO OCCUR BY THE END OF MARCH. | | | | | |
| OC RECOMMENDATION | 15-FEB-2014 | | | ACCEPTABLE | WILLIAMSJU |

**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: (b) (4) FEI: (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

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

Profile: DEVICE KIT ASSEMBLER OAI Status: NONE

STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

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

| | | | | | |
|--|-------------|-------------------------------------|------------|--|------------|
| 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 | (b) (6) | (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 | | (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 RECIEVED 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 RELAVTIVE 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 |

**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> | | | | | |
| 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: (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> | | | | | |

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|-------------------|-------------|---------------|--|------------|------------|
| 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> | | | | | |

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|-------------------|-------------|--|--|------------|---------|
| 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> | | | | | |

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|-------------------|-------------|--|--|------------|------------|
| 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 Addiction 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:

Submission(s) ReviewedDocument Date

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

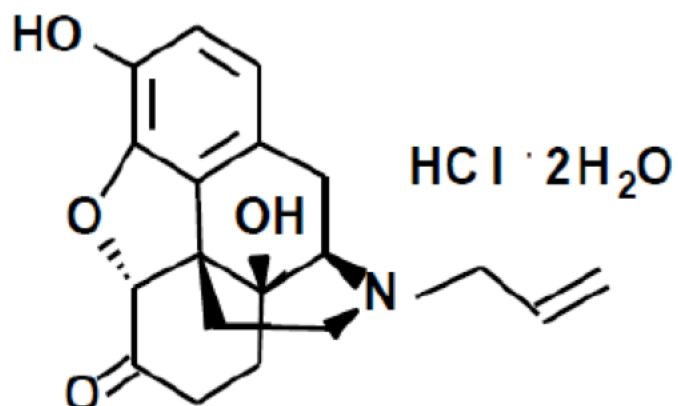
Naloxone Hydrochloride

Chemical Name(s)

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

Structure

CMC Review Data Sheet

**Molecular Formula**

C₁₉H₂₁NO₄·HCl·2H₂O

Relative Molecular Mass

(b) (4)

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | 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 |

¹ 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")

² 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:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|----------------------------------|---|-----------|------------------------|
| 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 (b) (4) list drug of naloxone HCl injection. The (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

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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
21st 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 | | |

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

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:

| A. COMPLETENESS OF FACILITY INFORMATION | | | | |
|---|---|-----|----|----------------------|
| | Parameter | Yes | No | Comment |
| 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) 1. Are all sites registered or have FEI #? | x | | |
| | 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.

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

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

| IMA CONCLUSION | | | | |
|-----------------------|--|------------|-----------|---|
| | Parameter | Yes | No | Comment |
| 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. | From a CGMP/facilities perspective, is the application fileable? 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

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

REVIEW AND APPROVAL (DARRTS)

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/s/

JUANDRIA WILLIAMS

02/26/2014

MAHESH R RAMANADHAM

02/28/2014