

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209862Orig1s000**

**ADMINISTRATIVE and  
CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 209862

SUPPL #

HFD #

Trade Name: Evzio, 2 mg

Generic Name: naloxone hydrochloride injection USP

Applicant Name: Kaleo, Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

#### 505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The study was a bioavailability study:

**The Applicant conducted study KA-900DV-05A in support of this application. Study 05A was a randomized, six-sequence, three-period pharmacokinetic (PK) bioavailability and dose proportionality study that evaluated a single injection of Evzio 2 mg, a single injection of Evzio 0.4 mg, and two injections of Evzio 0.4 mg given 2 minutes apart in 24 healthy adult volunteers.**

If it is a supplement requiring the review of clinical data but it is not an effectiveness

supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	16636	Narcan
NDA#	205787	Evzio, 0.4 mg
NDA#	208411	Narcan Nasal Spray

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed

only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was



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/s/  
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DIANA L WALKER  
10/19/2016

SHARON H HERTZ  
10/19/2016



NDA 209862

**GENERAL ADVICE**

kaleo, Inc.  
111 Virginia St.  
Suite 300  
Richmond, VA 23219

Attention: Glen Kelley  
Director Regulatory Affairs

Dear Mr. Kelley:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EVZIO (naloxone hydrochloride injection), 2 mg.

We also refer to our correspondence dated October 21, 2016, granting 12 months expiry for the 2 mg strength of Evzio (naloxone hydrochloride) Autoinjector. Upon further review of the submission dated July 15, 2016, we agree that sufficient stability data have been provided to support an expiry of 24 months for the 2 mg strength of Evzio (naloxone hydrochloride) Autoinjector.

If you have any questions, call Diana L. Walker, PhD, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Director  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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SHARON H HERTZ  
10/25/2016



NDA 209862

**GENERAL ADVICE**

kaleo, Inc.  
111 Virginia St.  
Suite 300  
Richmond, VA 23219

Attention: Glen Kelley  
Director Regulatory Affairs

Dear Mr. Kelley:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EVZIO (naloxone hydrochloride injection), 2 mg.

We also refer to the information request sent to you May 18, 2016, containing a request to provide a minimum of twelve months of long-term stability data for the three primary registration batches of the proposed 2 mg strength, as well as the statistical analysis, if needed, to support the proposed 24-month shelf life. We further refer to your commitment to submit this information by July 19, 2016.

A full response to the request for additional stability data to support a longer expiry has not been received, therefore, a 12-month expiry dating period has been granted for the 2 mg strength, approved on October 19, 2016. The expiry dating may be extended based upon the real time stability data at room temperature for the drug product manufactured in the proposed facility. We recommend a CBE-30 submission for the extension of the expiry dating period.

If you have any questions, call Diana L. Walker, PhD, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Director  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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SHARON H HERTZ  
10/21/2016

**PeRC Meeting Minutes  
September 21, 2016**

**PeRC Members Attending:**

Lynne Yao

Jacqueline Yancy

Hari Cheryl Sachs

Dianne Murphy

Gil Burckart

Raquel Tapia

Greg Reaman (did not review

NON RESPONSIVE

Wiley Chambers

John Alexander

Gettie Audain

Lily Mulugeta

Victor Baum

Robert 'Skip' Nelson

Gerri Baer

Ikram elayan

Adrienne Hornatko Munoz

Freda Cooner

Julia Pinto

Dionna Green

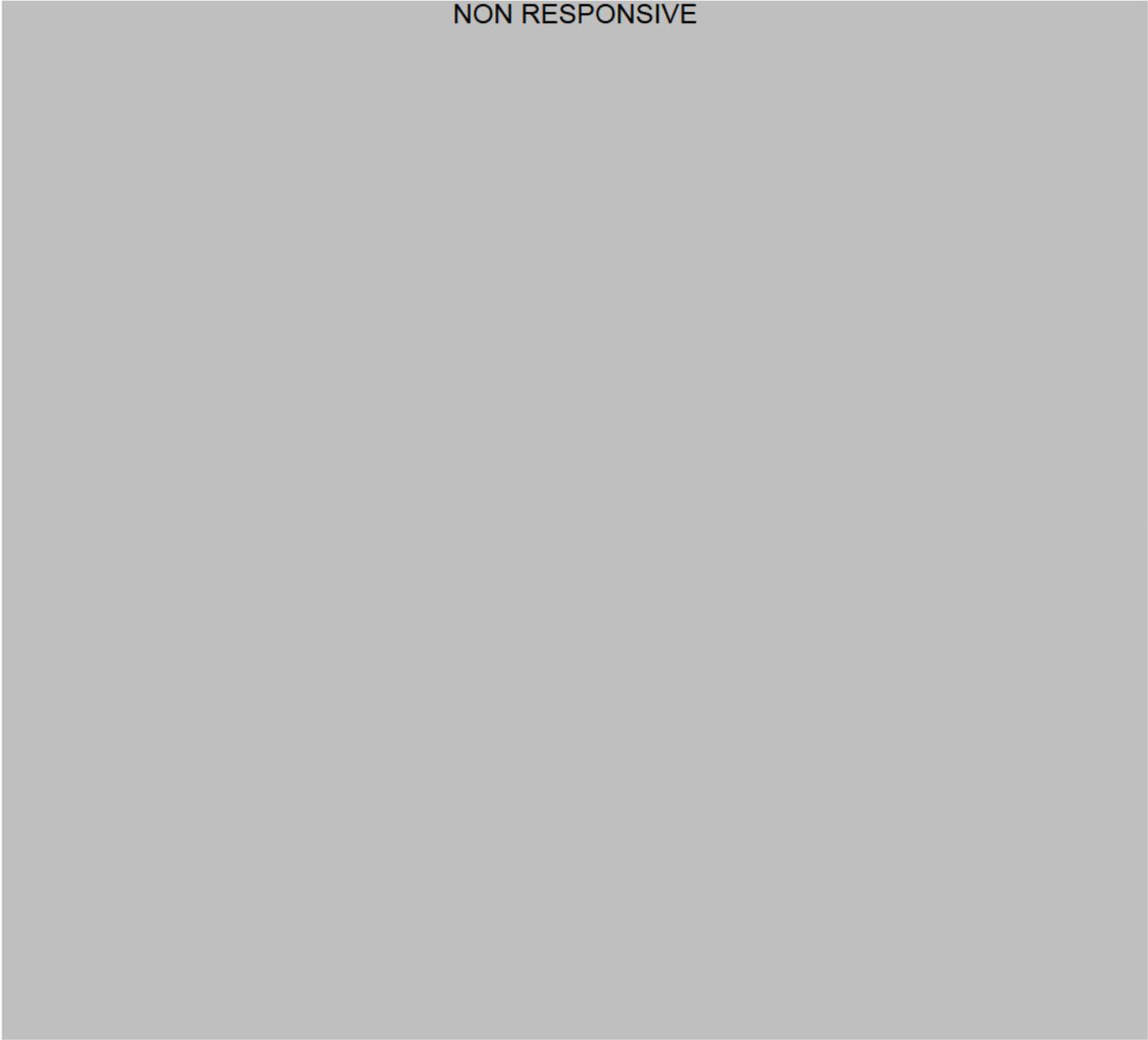
enda

9:00	NON RESPONSIVE				
9:30	NON RESPONSIVE				
9:45	NON RESPONSIVE				
9:55	NON RESPONSIVE				
10:15	NON RESPONSIVE				
10:25	NON RESPONSIVE				
10:40	NON RESPONSIVE				
10:55	NDA 205787/S007	Evzio (naloxone) Assessment	DAAAP	Diane Walker	Opioid overdose
11:10	NON RESPONSIVE				
	NON RESPONSIVE				
	NON RESPONSIVE				
	NON RESPONSIVE				
	NON RESPONSIVE				
	NON RESPONSIVE				
	NON RESPONSIVE				
	NON RESPONSIVE				

**Evzio (naloxone hydrochloride autoinjector, 2mg) Assessment**

- Proposed Indication: Opioid overdose
- This product triggers PREA as a new dosing regimen (new strength 2mg) and has a PDUFA goal date of October 19, 2016.
-  NON RESPONSIVE
- See discussion above. This product is intended to replace the currently existing 0.4 mg autoinjector.
- *PeRC Recommendations:*
  - PeRC agreed to the full assessment of the 2mg dosing regimen.

NON RESPONSIVE



1 Page has been Withheld in Full as Non responsive immediately following this page

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/s/  
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JACQUILINE A YANCY  
10/21/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley](#)  
**Subject:** Administrative Change for sNDA 205787/S-007 11Oct16  
**Date:** Tuesday, October 11, 2016 10:40:29 AM  
**Importance:** High

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Dear Glen,

I am emailing to let you know that the Division is making an administrative change to sNDA 205787/S-007. (b) (4)

(b) (4)  
the Division is administratively splitting this supplement from the original NDA into a new NDA. The new NDA will be **NDA 209862**, and will contain only the 2 mg strength submissions that originally went to the supplement (of course you can cross reference the original NDA and INDs, as usual). Right now, we are working with the electronic submissions team to see if you need to make a special submission(s) to the new NDA before resuming “business as usual”. It may be a day or two, but I will keep you informed, but in the meantime, please don’t make any new submissions to the S-007 or to the new NDA until I let you know. You can make normal submissions regarding the 0.4 mg strength to your old NDA if necessary (for example, annual reports, etc.). if you aren’t sure, please let me know and I will confirm for you.

As you might guess, because we are making this split, the labeling for this new NDA will reflect only the 2 mg strength. I will be contacting you in a separate email with labeling information requests.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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**From:** Glen Kelley [mailto:[Glen.Kelley@kaleopharma.com](mailto:Glen.Kelley@kaleopharma.com)]  
**Sent:** Thursday, July 28, 2016 1:06 PM  
**To:** Walker, Diana  
**Subject:** RE: sNDA 205787 S-007 General Information Request 25jul16

Dear Dr. Walker,

Unless FDA requires further information, I will submit the following response next week (when I will also submit the micro response). As a head’s up we will be submitting two OPDP submissions (one each professional and consumer) and the 9<sup>th</sup> PADER this afternoon.

Regards,

Glen

Informal response to request for information:

The request for information from FDA is listed below in **bold font** followed by kaleo, Inc.'s response.

**General Request**



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**From:** Walker, Diana [<mailto:Diana.Walker@fda.hhs.gov>]  
**Sent:** Monday, July 25, 2016 2:19 PM  
**To:** Glen Kelley <[Glen.Kelley@kaleopharma.com](mailto:Glen.Kelley@kaleopharma.com)>  
**Subject:** sNDA 205787 S-007 General Information Request 25jul16

Dear Glen,

I have received the following information request. Please submit your response to your sNDA

205787/S-007.

(b) (4)



Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
10/13/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** NDA 209862 Labeling Information request 11Oct16  
**Date:** Tuesday, October 11, 2016 11:45:24 AM  
**Attachments:** [EVZIO Trainer IFU revisions 11oct16.docx](#)  
[EVZIO IFU revisions 11Oct16.docx](#)  
**Importance:** High

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Dear Glen,

I have received comments on your container labeling and, due to the administrative split of your NDA to a new NDA containing only the 2 mg strength, I have revision requests for your patient labeling. We are still working on your other pieces of labeling (USPI and PPI) and these comments will be sent in a separate email.

Please revise the following documents:

- A. All Carton labeling and container labels
  - a. Remove all terminal zeroes and replace with whole numbers (2 mg instead of 2.0 mg) to prevent tenfold dosing errors.
  
- B. IFU- **see attached**
  - a. Remove all terminal zeroes and replace with whole numbers (2 mg instead of 2.0 mg) to prevent tenfold dosing errors.
  - b. This document was originally reviewed prior to the decision to administratively split the NDA. Therefore, disregard the revisions having to do with differentiating the 2 strengths, and **please revise this IFU to be a stand-alone IFU for the 2 mg strength**. Other comments are relevant.
  - c. Please check that text referring to figure numbers references the correct figures.
  - d. Please review the entire IFU for typos or other errors.
  
- C. Trainer – **see attached**
  - a. Revisions to remove the 0.4 mg strength
  - b. Revision to a table format
  - c. Please review the entire Trainer for typos or other errors.

As discussed in my previous email, as we are still waiting to determine the steps for electronic submission due to the administrative split, please do not submit the revised documents to your NDA at this time. **Please send the revised documents (Carton and container labels, IFU, Trainer) directly to me as soon as possible via email only.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
10/13/2016

## Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

**Complete the section(s) of this template that are relevant to your *current submission*.**

### **Definitions:**

**Deferral** – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

**Full Waiver** – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

**Partial Waiver** – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

**Pediatric Assessment** – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness

of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

**Pediatric Plan** – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

**Pediatric Population/Patient**- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

**PREA Pediatric Record/Pediatric Page** – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

## Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

### BACKGROUND

Please check all that apply:  Full Waiver  Partial Waiver  Pediatric Assessment  Deferral/Pediatric Plan

NDA#: 209862

PRODUCT PROPRIETARY NAME: EVZIO

ESTABLISHED NAME: Naloxone hydrochloride Autoinjector

APPLICANT/SPONSOR: Kaleo, Inc.

PREVIOUSLY APPROVED INDICATION/S: Evzio 0.4 mg Autoinjector is currently approved for the following indications:

(1)

- EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
- EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.
- EVZIO is not a substitute for immediate medical care.

(2) \_\_\_\_\_

(3) \_\_\_\_\_

**PROPOSED INDICATION:** This application was originally submitted as a supplement to NDA 205787, as sNDA 205787/S-007. There is no change in indication, there will only be the addition of a new 2mg dose. (b) (4)

\_\_\_\_\_ this supplement was converted into NDA 209862.

NDA STAMP DATE: April 19, 2016

PDUFA GOAL DATE: October 19, 2016

**Does this application provide for (If yes, please check all categories that apply and proceed to the next question):**

**NEW**  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?

**Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)**

Yes  No

**Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes  No**

**If Yes, PMR # \_\_\_\_\_ NDA # \_\_\_\_\_**

**Does the division agree that this is a complete response to the PMR? Yes  No**

**If Yes, to either question Please complete the Pediatric Assessment Template.**

**If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.**

#### **PeRC ASSESSMENT TEMPLATE**

**Please attach:**

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.**
- Pediatric Record – there are no studies so there is no pediatric record to attach.**

**Date of PREA PMR: n/a**

**Description of PREA PMR: n/a**

**Was Plan Reviewed by PeRC?  Yes  No** If yes, did sponsor follow plan?

**If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.**

**Indication(s) that were studied:**

**No pediatric clinical studies are proposed because pharmacokinetic (PK) studies in healthy, pediatric patients would involve more than minimal risk without the prospect of direct benefit to the population. Furthermore, PK studies cannot be conducted in a pediatric opioid overdose population because it is an immediately life-threatening condition and PK samples cannot be collected in the context of emergency treatment of the overdose, in addition to other ethical considerations that preclude conducting studies.**

**The Sponsor submitted a Pediatric Study Plan for Evzio 2 mg on September 22, 2015 which was agreed to by the Agency on October 16, 2015. The pediatric plan relies upon the safety and effectiveness of other naloxone hydrochloride products in the post-marketing setting as well as data available in the medical literature and clinical practice guidelines.**

**Drug information:**

- **Route of administration:** Intramuscular or subcutaneous Auto-Injection
- **Formulation:** Prefilled naloxone auto-injector
- **Dosage:** 0.4 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector (currently approved); 2 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector (proposed 2 mg)
- **Regimen:** Single dose for treatment of known or suspected overdose.

**Types of Studies/ Study Design:**

No new pediatric studies were conducted.

**Division comments and conclusions (Summary of Safety and Efficacy)**

**The Sponsor plans to rely on the currently approved labeling for the 0.4 mg auto-injector and published literature to support the pediatric labeling. The Division of Pediatric and Maternal Health (DPMH) has been consulted to assist in the review of the submitted pediatric information and the label.**

The DPMH consultant had the following additional comments: The Division of Pediatric and Maternal Health is likely to recommend approval of the 2 mg IM dose in all pediatric ages. (b) (4)

The utility of having multiple available naloxone doses (0.4 mg and 2 mg in this case) for any given naloxone drug product will be a key discussion point at the upcoming joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AC) and the Drug Safety and Risk Management AC scheduled for October 5, 2016.

**Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.**

The DPMH consultant had the following comments: Because the proposed naloxone dose of 2 mg IM is higher on a weight basis for neonatal patients, the Division of Pediatric and Maternal Health agrees with the sponsor's plan to enhance labeling language to consider weight-based dosing in neonates, in certain clinical settings that would allow for such dosing (such as professional healthcare settings), to avoid abrupt precipitation of opioid withdrawal. Other pediatric patients outside the neonatal period are most likely to require this product to reverse an acute opioid exposure and are, therefore, unlikely to be at risk for opioid withdrawal. The rest of the pediatric use information will likely be aligned with existing labeling for the 0.4 mg product (NDA 205787).

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/s/  
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DIANA L WALKER  
10/14/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** PMRs for sNDA 205787/S-007 06Oct16  
**Date:** Thursday, October 06, 2016 2:25:36 PM  
**Importance:** High

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Dear Glen,

This email contains the PMRs regarding device reliability studies that we plan to require for sNDA 205787/S-007, if or when it is approved, together with our proposed dates for completion of the milestones. We have proposed milestone timelines that are in line with very similar PMRs that were issued for similar studies for other products. Please send your concurrence to these PMRs and dates via a submission to your application as soon as possible. The portions in yellow will be updated prior to addition into an action letter once the specific numbers and dates are determined (the dates are based on the date of an approval action).

####-1 Establish reliability requirements for the combination product EVZIO (naloxone hydrochloride injection) and complete testing that verifies combination product reliability.

Draft Protocol Submission:	MM/YYYY (3 months post-approval)
Final Protocol Submission:	MM/YYYY (6 months post-approval)
Study Completion:	MM/YYYY (7 months after Final Protocol Sub)
Final Study Report:	MM/YYYY (2 months after Study Completion)

Please note the following considerations regarding the postmarketing requirement described above:

- 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 the functionality required for reliability.
- e. Define failure, as it relates to assessing the reliability requirements.

f. Provide data to verify the reliability specifications. The acceptable endpoints for this data should be linked to your definition of failure.

g. Devices assessed within the reliability data should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide a 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.

- Shipping
- Aging
- Storage orientation and conditions
- Vibration handling
- 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.

- Activation orientation
- Environmental temperature
- Simulated injection through clothing (e.g., pants, jeans, etc.)

i. Describe how manufacturing controls have been adequately implemented to achieve the reliability specification in the release product lots.

####-2 Establish procedures for monitoring reports of failure of the combination product EVZIO (naloxone hydrochloride injection) to activate or failure of the combination product to deliver the full-labeled dose. Provide interim and final reports to the NDA, which contain a detailed analysis of reported device failures (including reported malfunctions that did, as well as did not result in patient harm), full event narratives of the failure and any subsequent adverse events, and the results of root cause analysis performed for the reported failure.

Draft Protocol Submission: MM/YYYY (3 months post-approval)

Final Protocol Submission: MM/YYYY (6 months post-approval)

Interim Report Submission: MM/YYYY (14 months post-approval)

Final Report Submission: MM/YYYY (26 months post-approval)

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
10/14/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley](#)  
**Subject:** sNDA 205787 S-007 Devices Information Request 22sep16  
**Date:** Thursday, September 22, 2016 4:27:38 PM  
**Importance:** High

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Dear Glen,

I have received the following devices information request. Please respond to the following request via email as soon as possible, followed with a submission to your sNDA 205787 S-007 by **September 26, 2016**.

**You note that Registration Stability Lots MA002 and MA003 had individual samples fail to meet dispensing time specifications** [REDACTED] (b) (4)

[REDACTED]. **You state that you subsequently made a design change** [REDACTED] (b) (4)  
[REDACTED].

**You state that you have had no failures in the lots following this design change to your device. Provide more details regarding this design change (i.e. engineering drawings of before and after change, results of investigation, etc.) and provide a risk analysis regarding the design change. This risk analysis should describe all risks associated with the performance of the device after the design change and what testing has been completed to ensure the final finished combination product essential performance requirements have not been impacted by the change.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
10/14/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787 S-007 DMEPA Labeling Information Request 08sep16  
**Date:** Thursday, September 08, 2016 10:10:54 AM  
**Importance:** High

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Dear Glen,

I have received the following information request from our DMEPA team. Please provide a response by 12pm September 9, 2016, via email. You can include this later with your next submission to your sNDA 205787 S-007.

**Regarding the labeling differentiation study, clarify how much time was given to the laypeople participants to explore the carton and auto-injector and how much time elapsed between exploration and Task 1.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
09/08/2016

## Walker, Diana

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**From:** Walker, Diana  
**Sent:** Wednesday, August 31, 2016 10:22 AM  
**To:** Glen Kelley (glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787 S-007 Clinical Information Request 31aug16

Dear Glen,

I have received the following clinical information request. Please respond to the following request with a submission to your sNDA 205787 S-007.

For Study KA-900DV-05A, provide clarification for Table 12-2 (CSR, p. 65) regarding Skin and Subcutaneous Tissue Disorders SOC (preferred term, Erythema). The table shows that erythema was experienced by two subjects in Treatment A, five subjects in Treatment B, and one subject in Treatment C. You then provided a clarification for three subjects (113, 116, and 123 in Table 12-3, CSR, p. 70) in which there was a discrepancy between when these subjects received the treatment and when the adverse event of erythema was experienced. However, this revised information does not appear to be reflected in Table 12-2.

1. Clarify if Table 12-2 is accurate (specifically with regard to the preferred term, erythema) and, if not, provide an accurate table which takes into account the corrections for the three subjects previously described.
2. In addition, correct the pooled safety tables, if needed, for the preferred term, Erythema and resubmit the corrected tables.

**Table 12-2 Number (Percentage) of Subjects with Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment**

System Organ Class Preferred Term	Treatment A N = 24 n (%)	Treatment B N = 24 n (%)	Treatment C N = 24 n (%)
<b>General Disorders and Administrative Site Conditions</b>	<b>1 (4.2)</b>	<b>1 (4.2)</b>	<b>0</b>
Catheter site swelling	1 (4.2)	0	0
Injection site bruising	0	1 (4.2)	0
<b>Nervous System Disorders</b>	<b>1 (4.2)</b>	<b>1 (4.2)</b>	<b>0</b>
Dizziness	0	1 (4.2)	0
Headache	1 (4.2)	0	0
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>2 (8.3)</b>	<b>5 (20.8)</b>	<b>2 (8.3)</b>
Dermatitis contact	0	0	1 (4.2)
Erythema <sup>†</sup>	2 (8.3)	5 (20.8)	1 (4.2)

N = number of subjects exposed to treatment; n = number of subjects with treatment emergent adverse events; (%) =  $n/N \times 100$ ; TEAE = treatment-emergent adverse event

<sup>†</sup> Adverse events of erythema were assigned to a treatment group based on the start date and time of the erythema and not based on the injection site location identified in the adverse event description.

Treatment A = 0.4 mg naloxone (single 0.4 mg injection); Treatment B = 0.8 mg naloxone (two 0.4 mg injections); Treatment C = 2.0 mg naloxone (single 2.0 mg injection)

Data source: Section 14.3, Table 14.3.1.2

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
08/31/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787 S-007 Clinical Information Request 30aug16  
**Date:** Tuesday, August 30, 2016 8:47:26 AM

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Dear Glen,

I have received the following clinical information request. Please respond to the following request with a submission to your sNDA 205787 S-007.

**You have not submitted a 120-day safety update. Provide any additional safety information relevant to sNDA 205787 (Evzio 2 mg) that you have received since the initial submission on April 19, 2016. State if there is no new safety information.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
08/30/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787 S-007 Maternal Health Information Request 25aug16  
**Date:** Thursday, August 25, 2016 10:08:28 AM  
**Importance:** High

---

Dear Glen,

I have received the following information request from our maternal health team. Please respond with a submission to sNDA 205787 S-007 as soon as possible.

**Provide a cumulative summary from the pharmacovigilance database of exposures during pregnancy and lactation and reports of effects on reproductive potential.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
08/25/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** NDA 205767 Device Information Request 05aug16  
**Date:** Friday, August 05, 2016 9:20:06 AM  
**Importance:** High

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Dear Glen,

I have received the following information request from our devices review team. Please submit the following information as soon as possible, or by close of business on the following dates: August 8, 2016 for #1 and 2 and August 11, 2016 for #3 and 4.

You can send your responses via email, and follow with an official submission to your NDA.

Please respond to the following questions:

1. You state in Table 3.2.D.2.8-1: Stability Data for Naloxone Auto-Injector that the Accelerated Aging Study for (b) (4) Lot F0119415BB was completed with storage conditions of (b) (4), which is equivalent to 2 years of simulated aging. However, in Table 3.2.D.2.8.2-11: Device Performance Stability Data for Batch F0119415BB Stored at Accelerated Stability Condition you state that the storage condition was (b) (4). Explain this discrepancy and provide a rationale as to how the tested accelerated storage conditions is equivalent to 2 years of simulated aging.
2. We note that you provided stability data from Batch F0119415BB in support of the device constituent's performance with the proposed 2 mg dose. Describe the differences, if any, between the Commercial Product referenced in Table 3.2.P.8.1.3-7 and the (b) (4) Registration Batch referenced in Table 3.2.P.8.1.3-5 of the document titled Stability Summary and Conclusion under eCTD Module 3.2.P.8.
3. Provide updated device performance stability data at the 12-month time point for Batch F0119415BB currently undergoing long-term conditioning with an initiation date of July 22, 2015. Provide a statistical rationale for this data supporting the 2 year shelf-life of the combination product (i.e. no degradation of the essential performance requirements of the device).
4. Due to the intended use of your combination product, the Agency expects your device to meet a high threshold of reliability. Therefore the Agency requests that you provide the following information either under this supplement or as a post-market requirement:
  - a. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:
    - i. 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 preconditioning to elements outlined within (iv), below. The reliability requirements should be verified with a high degree of statistical confidence.

ii. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.

iii. Perform a test to verify the reliability requirements specified in above.

iv. Devices assessed within the reliability test 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.

1. Shipping

2. Aging

3. Storage orientation and conditions

4. Vibration handling

5. Shock handling (e.g., resistance to random impacts, such as being dropped)

v. 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.

1. Activation orientation

2. Environmental temperature

b. 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.

If you have any questions, please feel free to contact me.

Warm regards, Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
08/09/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787 S-007 General Information Request 25jul16  
**Date:** Monday, July 25, 2016 2:18:35 PM

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Dear Glen,

I have received the following information request. Please submit your response to your sNDA 205787/S-007.



Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
07/25/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787 S-007: Microbiology Information Request 21jul16  
**Date:** Friday, July 22, 2016 9:42:49 AM

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Dear Glen,

I have received the following information request from our Product Quality/Microbiology review team. Please submit responses to these information requests to your NDA as soon as possible or no later than **August 22, 2016**.

**Provide the following information or a reference to its location in sNDA 205787/S-007:**

1. With regard to the (b) (4):



Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
07/25/2016



NDA 205787/S-007

**FILING COMMUNICATION –  
FILING REVIEW ISSUES IDENTIFIED**

kaleo, Inc.  
111 Virginia St.  
Suite 300  
Richmond, VA 23219

Attention: Glen Kelley  
Director Regulatory Affairs

Dear Mr. Kelley,

Please refer to your supplemental New Drug Application (sNDA) dated and received April 19, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for EVZIO (naloxone hydrochloride injection).

We also refer to your amendments dated May 6 and June 1, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is October 19, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 28, 2016.

During our filing review of your application, we identified the following potential review issues:

1. Your prescribing information (PI) must comply with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements [see *Content and Format of*

*Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014), codified at 21 CFR 201.56 and 201.57(c)(9)]. Although you have submitted the PI in PLLR format, the submission must include a review and summary of the available published literature regarding drug use in pregnant and lactating women, which should be located in Module 1. Submit the integrated summary to your NDA as soon as possible. Refer to the *draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). In addition, conduct a thorough review of the existing nonclinical literature for naloxone's effects on reproduction and development in your drug product and propose revised text for Section 8 of the labeling if additional relevant data are identified. Copies of all referenced citations must be submitted to the NDA. Nonclinical information should be located in Module 2 (summaries) and Module 4 (literature references).

2. Although you did not provide a separate annotated label, you have provided annotation comments in the Word version of your package insert. Your annotated labeling contains



3. We remind you of the commitment in your June 1, 2016, submission to submit the following requested information no later than July 19, 2016.
  - a. Provide a minimum of twelve months of long-term stability data for the three primary registration batches of the proposed 2 mg strength, as well as statistical analysis (if needed) to support the proposed 24-month shelf life.
  - b. Provide three months stability results for Lot (b) (4) under both long-term and accelerated storage conditions.
  - c. Provide a copy of the proposed master batch record for the proposed 2 mg strength.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

## **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted a pediatric assessment with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Diana L. Walker, PhD, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Director  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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SHARON H HERTZ  
06/09/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787 S-007Administrative Information Request 07jun16  
**Date:** Tuesday, June 07, 2016 1:42:56 PM

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Dear Glen,

I have not been able to locate your debarment certification in your sNDA 205787 S-007 submission.

Please point me to the location of this document within the submission, or provide this document as an amendment to your supplement as soon as possible.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
06/08/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787/S-007 Clinical Information Request 19may16  
**Date:** Thursday, May 19, 2016 10:08:35 AM  
**Importance:** High

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Dear Glen,

I have received an information request from our Clinical review team. Please provide the requested information by **June 9, 2016**.

**1) Your application must contain the required Module 2 summaries, including the Summary of Clinical Effectiveness (SCE) and Summary of Clinical Safety (SCS). Submit these to your sNDA as soon as possible. If you believe that the ISE and ISS otherwise meet the requirements for an SCE and SCS, respectively, you may submit a cross-reference and link to these documents in the Module 2 summaries.**

**2) You reference the previously submitted quarterly periodic adverse drug experience reports (PADERs) and state that, “[t]he most recent review of the NAI post-marketing safety database was conducted through January 2, 2016 and did not show any new or significant post-marketing reports of adverse events.” However, this is not a sufficient postmarketing analysis for your sNDA. You must conduct a comprehensive safety analysis of the postmarketing data for your 0.4 mg naloxone product and submit that to the sNDA, including an assessment of reported adverse events, events where the product was ineffective, device failures, and events in the pediatric population.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
06/08/2016

**From:** [Walker, Diana](#)  
**To:** [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** sNDA 205787/S-007 CMC Information Request 18may16  
**Date:** Wednesday, May 18, 2016 3:14:27 PM  
**Importance:** High

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Dear Glen,

I have received an information request from our Chemistry, Manufacturing, and Controls review team. Please provide the requested information by **June 18, 2016**. If you cannot provide the requested information by this date, submit a statement committing to provide the information by no later than July 19, 2016.

- 1. Provide a minimum of twelve months of long-term stability data for the three primary registration batches of the proposed 2 mg strength, as well as statistical analysis (if needed) to support the proposed 24-month shelf life.**
- 2. Provide three months stability results for Lot (b) (4) under both long-term and accelerated storage conditions.**
- 3. Provide a copy of the proposed master batch record for the proposed 2 mg strength.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
06/08/2016



sNDA 205787/S-007

**ACKNOWLEDGMENT --  
PRIOR APPROVAL SUPPLEMENT**

kaleo, Inc.  
111 Virginia St.  
Suite 300  
Richmond, VA 23219

Attention: Glen Kelley  
Director Regulatory Affairs

Dear Mr. Kelley:

We have received your supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 205787  
**SUPPLEMENT NUMBER:** S-007  
**PRODUCT NAME:** EVZIO (naloxone hydrochloride injection)  
**DATE OF SUBMISSION:** April 19, 2016  
**DATE OF RECEIPT:** April 19, 2016

This supplemental application proposes addition of a new 2.0 mg strength.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 18, 2016, in accordance with 21 CFR 314.101(a).

If the application is filed, the User Fee goal date will be February 19, 2017.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

## **FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

## **SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia, and Addiction Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Diana L. Walker, PhD  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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DIANA L WALKER  
05/02/2016



IND 112292

**MEETING MINUTES**

kaleo, Inc.  
111 Virginia Street, Suite 300  
Richmond, VA 23219

Attention: Glen Kelley  
Director, Regulatory Affairs

Dear Mr. Kelley:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for EVZIO (naloxone hydrochloride injection).

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2014. The purpose of the meeting was to discuss the development of a new naloxone autoinjector that provides a higher dose than EVZIO.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Diana L. Walker, PhD  
Sr. Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

### MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-sNDA

**Meeting Date and Time:** December 8, 2014, 2:30 p.m. (Eastern)  
**Meeting Location:** Teleconference

**Application Number:** IND (b) (4)  
**Product Name:** EVZIO (naloxone autoinjector)  
**Indication:** Emergency treatment of known or suspected opioid overdose  
**Sponsor/Applicant Name:** kaleo, Inc.

**Meeting Chair:** Joshua Lloyd, MD, Clinical Team Leader, DAAAP  
**Meeting Recorder:** Diana Walker, PhD, Sr. Regulatory Project Manager, DAAAP

Industry Representatives	Title
Frank Blondino	Director, Drug Development
Evan Edwards	Vice President, Product Development
Eric Edwards	Chief Medical Officer
Ronald D. Gunn	Chief Operating Officer
Glen Kelley	Director, Regulatory Affairs
<b>FDA</b>	<b>Title</b>
Sharon Hertz, MD	Acting Division Director, DAAAP
Joshua Lloyd, MD	Clinical Team Leader, DAAAP
Ramesh Ragavachari, PhD	Branch Chief, ONDQA
Don Klein, PhD	Acting CMC Lead, ONDQA
John Duan, PhD	Team Leader, Biopharmaceutics
Assadollah Noory, PhD	Biopharmaceutics Reviewer
Daniel Mellon, PhD	Pharmacology/Toxicology Supervisor
Newton Woo, PhD	Pharmacology/Toxicology Team Leader (Acting)
Carlic Huynh, PhD	Pharmacology/Toxicology Reviewer
Yun Xu, PhD	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP2)
Irene Z. Chan	Director, DMEPA
Millie Brahmabhatt, PharmD	DMEPA Reviewer
Juandria Williams, PhD	CDER Compliance
Lana Shiu, MD	Reviewer, DAGRID, ODE, CDRH
Beverly Friedman	User Fee Staff, Office of Management
Peter Chen, RPh	User Fee Staff, Office of Management
Lisa Skarupa	Safety Regulatory Project Manager, OSE
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

## 1.0 BACKGROUND

- a. EVZIO (naloxone hydrochloride injection) 0.4 mg autoinjector was approved under NDA 205787 on April 3, 2014.
- b. kaleo, Inc. is proposing a higher dose of naloxone than the current 0.4 mg dose that is contained in each EVZIO and has designed this second naloxone autoinjector (NAI) product (i.e., NAI-HP) to utilize the same device constituent and dosing volume as EVZIO, but to contain a drug constituent at a higher concentration of naloxone HCl.
- c. NAI-HP is similar to EVZIO, but it contains a naloxone solution at 5 mg/mL rather than the 1 mg/mL drug solution contained in EVZIO (delivering 2 mg versus the 0.4 mg currently in EVZIO).
- d. The purpose of this meeting is to discuss the development program for the proposed higher concentration product.
- e. The Sponsor received the Agency's preliminary responses to the current meeting questions on December 5, 2014, via email. The Sponsor sent the Division their responses to the preliminary responses on December 8, 2014, indicating which questions they would focus on during the meeting.
- f. The Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

## 2.0 DISCUSSION

*Question 1. Does the FDA agree that NAI-HP should be submitted as a supplement to NDA 205787?*

**Agency Response:**

**Yes, we agree that the addition of a new dose should be submitted as a supplement to your previously approved NDA.**

Discussion

There was no further discussion of this question.

*Question 2. Does the FDA agree that the proposed NAI-HP sNDA does not require a PDUFA fee for its review?*

**Agency Response:**

User fees will be assessed for supplements containing clinical safety or efficacy data that are required to form the primary basis for approval. Refer to guidance for industry: *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (Bundling Guidance)*, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079320.pdf>

We have the following comments based on your proposal:

- You propose, concurrent with the proposal for a 2 mg product, a change to the labeling that describes that the 2 mg product is intended to be used (b) (4)  
(b) (4)  

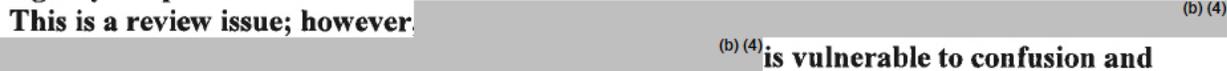
- You are required to address the safety and efficacy of the higher dose in pediatric patients (refer to our response to Question 15). Even if you address this request by providing a reanalysis of the literature that you previously submitted to the original NDA, a user fee may be assessed, as a reanalysis of a previously submitted literature report is considered new clinical data.

Discussion

There was no further discussion of this question.

*Question 3. Does the FDA agree that the putting the dose prominently in the upper face of the carton and changing the carton color scheme is sufficient to distinguish the NAI-HP carton from the Evzio Carton?*

**Agency Response:**

**This is a review issue; however,** (b) (4)  
 (b) (4) **is vulnerable to confusion and product selection errors. Carefully evaluate the risk for product selection errors, and ultimately consider a color scheme for the device label and case and carton labeling for NAI-HP that is sufficiently different to minimize this risk.**

Discussion

There was no further discussion of this question.

*Question 4. Does the FDA agree that the different color scheme of the dose and color schemes are sufficient to distinguish the NAI-HP device and outer case labels from the Evzio Device and Outer Case labels?*

**Agency Response:**  
**See response to Question 3.**

Discussion

There was no further discussion of this question.

**Question 5.** *Can the FDA review and approve the labeling provided in Attachment 3 before submission of the sNDA?*

**Agency Response:**

**No, we do not agree. Labeling will be reviewed and, if necessary, comments will be provided during the review cycle for the sNDA. Labeling is only considered approved and final at the time of approval.**

Discussion

There was no further discussion of this question.

**Question 6.** *Does the FDA agree that the stability program can be conducted using* (b) (4)  
(b) (4)

**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.**

Discussion

There was no further discussion of this question.

**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 NAI-HP?*

**Agency Response:**

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

Discussion

There was no further discussion of this question.

**Question 8.** *The Does FDA agree that three registration batches of the 5 mg/mL naloxone HCl (2.0 mg dosage form) and 1 registration batch of the 1 mg/mL (0.4 mg*

*dosage form) will be adequate to support the approval of these two dosage forms at (b) (4)?*

**Agency Response:**

**This is acceptable. Provide supportive data if available.**

Discussion

There was no further discussion of this question.

*Question 9. Does the FDA agree that an extractable and leachables evaluation for the proposed NAI-HP container closure system is not necessary?*

**Agency Response:**

**As you are not proposing to alter the container closure system, we agree that new extractable studies are not necessary. However, the new drug product solution is a higher concentration, which may result in an increase in leachables over the course of your stability studies. Therefore, you must monitor for leachables over the course of your stability studies with the new drug product formulation and provide a revised risk assessment for any leachable that exceeds that previously reported for the original drug product formulation. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure for a chronic indication or be adequately qualified for safety. From a genetic toxicology perspective, we will allow up to 120 mcg/day for an acute indication for most potentially genotoxic impurities. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.**

**We acknowledge the ongoing leachable study (24 months at 25 C/60%RH) that is part of the NAI stability program. In the event unsafe leachables are detected, the NAI-HP stability program must be revised accordingly.**

Discussion

There was no further discussion of this question.

*Question 10. Assuming that no differences in stability trends are observed, does the FDA agree (b) (4)*

**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.**

Discussion

There was no further discussion of this question.

*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 post-approval. The Agency agreed with the Sponsor's proposal.

*Question 12.*

(b) (4)

**Agency Response:**

**No, we do not agree. You propose a change in drug concentration from 1 mg/mL to 5 mg/mL using the same delivery device without adjustment to the device design. Provide dose accuracy testing data to support the review and approval of the new drug concentration. As such, also provide updated software testing documentation related to the new drug concentration.**

Discussion

There was no further discussion of this question.

*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.**

Discussion

There was no further discussion of this question.

*Question 14. If Device and Outer Case labels are not approved prior to submission of the sNDA, does the FDA agree that this sNDA can be reviewed and approved prior to completion of the PPQ protocol, with the understanding that no commercial distribution will occur until these validation activities are completed?*

**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 proposal appears to be acceptable.**

**FDA does not specify or require completing full-scale process validation batches before the approval of the application. However, full-scale process validation studies are required to be completed prior to distribution of the commercial product. Prior to marketed product distribution, you must justify and confirm earlier process design and development work for their proposed manufacture of the device containing higher concentration of drug constituent at commercial scale. You must provide justification for your process parameters, component characteristics, and how these relate to the final product attributes, demonstrated at commercial scale.**

Discussion

There was no further discussion of this question.

*Question 15. Does the FDA agree that no additional clinical studies would be required to support review and approval of the NAI-HP 2.0 mg dosage form?*

**Agency Response:**



The proposed application will trigger PREA and the 2 mg dose may be appropriate as the initial dose in all pediatric patients as well. Therefore, submit a review and analysis of the published literature, leveraging existing pediatric information in approved labeling for your reference product, to evaluate the safety and effectiveness of the 2 mg dose of your product in all pediatric populations (similar to what you did to support pediatric labeling for the 0.4 mg dose). We recommend including this data with your sNDA submission. Alternatively, you may request and submit justification for a deferral of this assessment. Refer to Additional Comment 4 below regarding your initial pediatric study plan (iPSP) in support of this application.

Although you may qualify for a biowaiver for the proposed 2 mg dose, and, therefore, a clinical bioavailability/bioequivalence (BA/BE) study would not be required if the biowaiver is granted for this dose, we strongly recommend that you perform a pharmacokinetic (PK) study to better understand the PK profile of your product and to inform labeling and prescribers. The biowaiver decision will be made during the sNDA review and will be based on the justification you provide in the sNDA submission. Submit a formal request for waiver of the BA/BE study and provide documentation regarding the need for the higher strength, the safety of the higher dose, and the linearity of the pharmacokinetics over the therapeutic dose range. This documentation may be from published literature or the studies you conducted.

#### Discussion

The Sponsor sent the following statement to the Agency via email on December 8, 2014, and read the following questions during the meeting:

*Kaléo appreciates the Division's advice regarding the possibility that the 2.0 mg strength may be suitable for use in all populations, including certain pediatric populations, as an initial dose. Kaléo intends to seek approval of NAI-HP for use in all populations in which it is safe and effective.*

*Kaléo is considering the Divisions recommendation to perform a PK profiling study and requests FDA's responses to the following clarifying questions:*

**Question 15A.** *In general, does FDA believe a 2-period, 2-treatment (Evzio 0.4 mg and NAI-HP 2.0 mg), crossover pharmacokinetic (PK) study in 8 to 12 subjects will be sufficient to inform labeling and prescribers and provide the information recommended by FDA pertaining to linearity of the pharmacokinetics over the therapeutic dose range?*

The Agency stated agreement with the Sponsor's proposal and added that the minimum final analyzable sample size is 12 subjects for each treatment group to establish dose proportionality. Furthermore, the Sponsor should include a dose normalized AUC and  $C_{max}$  to target the 80 - 125 range for the 90% confidence intervals in the dose proportionality linearity analysis. The Agency requested this analysis; however, 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. The Agency stated that the Sponsor must use the final to-be-marketed product in the PK study.

The Sponsor agreed and will provide a justification for the final sample size with the submission. The Sponsor also stated that they plan to use the final to-be-marketed product in the PK study and will use cartridges containing the to-be-marketed product loaded into devices for all studies (i.e., dose proportionality and stability studies). The Agency found the Sponsor's proposal acceptable.

The Agency would normally require a nonclinical study to examine local tolerability, as the proposed product represents a higher concentration of naloxone. However, if the Sponsor includes a clinical evaluation of local tolerability at the site of administration in the PK study, an animal study would not be required. The Sponsor agreed to include a clinical evaluation of local tolerability in their study design and will submit the protocol to the Agency for review.

***Question 15B.** Is FDA willing to review the final proposed protocol design for this PK study and provide comments?*

The Agency agreed to review the proposed protocol and will try to expedite this review, within reason based on current work load, in order to provide comments.

#### **Additional Comments**

1. **As was conducted for the NAI (EVZIO), the following should be completed for the NAI-HP:**
  - a. **Photostability study**
  - b. **Temperature cycling study**
  - c. **In the supplement, provide a comparison of the NAI (EVZIO) and NAI-HP data**
2. **Your proposed new drug product formulation contains a higher concentration of naloxone than previously approved. Therefore, you must provide adequate characterization of the local tissue reaction following injection of the drug product. This may be completed via a nonclinical toxicology study in a single species. The study should include a histopathological evaluation of the injection site both at an acute time point (e.g., 24 hours post injection) and a delayed observation (generally 14 days post injection). Alternatively, if you conduct a human PK study, you can evaluate the potential for local toxicity in that context.**
3. **We remind you that for the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:**

- a. **You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
  - b. **In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14 days duration should be completed.**
4. **PREA requires that all NDAs, BLAs, or supplemental applications for a new active ingredient (includes new combination), new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless a waiver or deferral has been obtained. A pediatric assessment contains data gathered from pediatric studies and/or other data that are adequate (e.g., published literature) to: 1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and 2) support dosing and administration for each pediatric subpopulation for which the product has been assessed to be safe and effective. FDA is encouraging sponsors to submit their plans for conducting the required pediatric assessments as early as possible in the drug development process and to discuss these plans with FDA at critical points in the development process for a particular drug or biologic.**

**Submit the initial Pediatric Study Plan (iPSP) as soon as possible or, at a minimum, 210 days prior to your planned sNDA submission date outlining how you plan to meet the PREA requirements. The plan should address all relevant pediatric subpopulations and the appropriateness of your formulation for use in all of those subpopulations. Furthermore, it should address whether and, if so, under what grounds, you plan to request a waiver or deferral of pediatric studies.**

**Refer to draft guidance for industry: *How to Comply with the Pediatric Research Equity Act*, available at**

**<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079756.pdf>**

**Refer to the guidance for industry: *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*, available at**

**<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>**

#### Discussion

There was no further discussion of these comments.

**3.0 ACTION ITEMS**

- a) The Agency agreed to review a PK study protocol and to try to expedite feedback.

**4.0 ATTACHMENTS AND HANDOUTS**

None.

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/s/  
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DIANA L WALKER  
12/23/2014