

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209862Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209862	NDA Supplement #: N/A	Efficacy Supplement Type: N/A
Proprietary Name: Evzio Established/Proper Name: naloxone hydrochloride injection USP Dosage Form: autoinjector Strengths: 2.0 mg (2.0 mg/0.4 mL)		
Applicant: kaleo, Inc.		
Date of Receipt: April 19, 2016		
PDUFA Goal Date: October 19, 2016	Action Goal Date (if different): n/a	
RPM: Diana Walker		
Proposed Indication(s): EVZIO is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and is intended for immediate administration as emergency therapy in settings where opioids may be present.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>published literature</i>	<i>Nonclinical pharmacology, pharmacokinetics, and toxicology. Also human clinical pharmacology, safety and efficacy for pediatric use</i>
<i>NDA 016636: Narcan (naloxone hydrochloride)</i>	<i>FDA's previous finding of safety and effectiveness (clinical and nonclinical)</i>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Kaleo Inc submitted a 505(b)(2) NDA (NDA 205787) for EVZIO, which relied on the Agency’s previous findings of safety and effectiveness for the listed drug, Narcan (NDA 016636), by demonstrating bioequivalence to the listed drug in a pharmacokinetic study. NDA 205787 was approved April 3, 2014.

The Sponsor originally submitted this application as a supplement to NDA 205787, seeking to add a new dose, and including a clinical pharmacokinetic study evaluating dose proportionality of the approved Evzio 0.4 mg to the proposed Evzio 2.0 mg. This supplement was administratively converted to an NDA, NDA 209862.

The Applicant also performed an analysis of the literature to support the safety of Evzio 2.0 mg from a clinical perspective in the pediatric population.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “**NO**”, proceed to question #5.

If “**YES**”, list the listed drug(s) identified by name and answer question #4(c).

Narcan (naloxone hydrochloride)

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If “**NO**,” proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Narcan (naloxone hydrochloride)	NDA 016636	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “N/A”.

*If “**NO**”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

NDA 016636: Narcan (naloxone hydrochloride)

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The original NDA 205787 for Evzio (naloxone HCl; 0.4 mg), a pre-filled autoinjector, provided for a new dosing regimen in pediatrics (weight-based to fixed dose) and was a new drug-device combination (Type 3/Type 4 new NDA). This current NDA proposes adding a 2 mg dose.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

Related indication (reversal of opioid overdose) but slightly different to reflect intended setting of use (i.e., community/out-of-hospital)

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

If this application relies only on non product-specific published literature, answer "**N/A**"
If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): Narcan NDA 16636 and generics

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): ***Narcan Nasal Spray NDA 208411***

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

DIANA L WALKER
10/20/2016



Food and Drug Administration
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: October 18, 2016

From: Tamara Johnson, MD, MS
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne Yao, MD
Division Director
Division of Pediatric and Maternal Health

To: Division of Anesthetics, Analgesia and Addiction Products

Drug: Evzio (naloxone hydrochloride injection)

NDA: 209862

Applicant: Kaleo, Inc.

Drug Class: opioid antagonist

Indication: For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression; intended for immediate administration as emergency therapy in settings where opioids may be present.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Submission Date: April 19, 2016

Consult Date: June 28, 2016

Consult Request: DAAAP requests assistance in reviewing the labeling for compliance with the PLLR format.

PURPOSE

The purpose of the memorandum is to acknowledge the input of the Division of Pediatric and Maternal Health (DPMH) on labeling recommendations in order to bring the Evzio labeling in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format and content requirements.

BACKGROUND

The Pregnancy and Lactation Labeling Rule

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect.¹ The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of the Evzio labeling for compliance with the PLLR. DPMH labeling recommendations were conveyed to DAAAP at the September 19, 2016 labeling meeting. DPMH agrees with the PLLR labeling for Evzio and refers the reader to the final NDA action for the final labeling.

¹ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

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

/s/

TAMARA N JOHNSON
10/18/2016

LYNNE P YAO
10/19/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 209862
Product Name: EVZIO (Naloxone hydrochloride) auto-injector, 2 mg

PMR/PMC Description: PMR 3135-1

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

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	<u>01/2017</u>
	Final Protocol Submission:	<u>04/2017</u>
	Study/Trial Completion:	<u>11/2017</u>
	Final Report Submission:	<u>01/2018</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Clinical studies and batch analysis performed with the device, although conducted in limited numbers, demonstrated favorable rates of successful delivery.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has not demonstrated the reliability of the combination product in delivering the therapy (i.e. high population sample activation studies). The sponsor has not demonstrated the ability of the device to activate reliably after exposure to all relevant preconditions, including effects of storage, transportation, and environmental conditions up to the labeled date of expiry.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a (b) (4) study. It will examine the reliability of the combination product after simulated exposure to storage, shipping, and in-use conditions. A separate study will be executed to monitor for unreliable product in the field.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Device reliability testing studies
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 209862
Product Name: EVZIO (Naloxone hydrochloride) auto-injector, 2 mg

PMR/PMC Description: PMR 3135-2

Conduct case study analysis of 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. Perform detailed analyses of reported device failures (including reported malfunctions that did, as well as did not result in patient harm). Reports should include a full narrative description of the failure, any subsequent adverse events, the results of root cause analysis performed for the reported failure, and a description of your procedures for monitoring and analyzing the reports.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	<u>01/2017</u>
	Final Protocol Submission:	<u>04/2017</u>
	Study/Trial Completion:	<u>12/2017</u>
	Final Report Submission:	<u>12/2018</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Clinical studies and batch analysis performed with the device, although conducted in limited numbers, demonstrated favorable rates of successful delivery.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has not demonstrated the reliability of the combination product in delivering the therapy (i.e. high population sample activation studies). The sponsor has not demonstrated the ability of the device to activate reliably after exposure to all relevant preconditions, including effects of storage, transportation, and environmental conditions up to the labeled date of expiry.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

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– **Which regulation?**

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– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a (b) (4) study. It will examine the reliability of the combination product after simulated exposure to storage, shipping, and in-use conditions. A separate study will be executed to monitor for unreliable product in the field.

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- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
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 - Other (provide explanation)
Device reliability testing studies
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

DIANA L WALKER
10/19/2016

JUDITH A RACOOSIN
10/19/2016

Date: October 18, 2016

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

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

Office of combination products at combination@fda.gov

RPM: Diana Walker

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

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

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

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

Application # sNDA205787/S007

Consult # ICC1600357

Product Name: EVZIO (Naloxone autoinjector), 2 mg

**Combination Product
Intended Use:**

Evzio (Naloxone Autoinjector (NAI)) is indicated

(b) (4)

Pre-Approval Inspection: NO

Documentation Review: No Additional Information Required

Final Recommendation: APPROVAL

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

PRODUCT DESCRIPTION

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

REGULATORY HISTORY

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

Kaléo Inc. 111 Virginia St, Suite 300 Richmond, VA 23229 FEI # 3007135538	<ul style="list-style-type: none">• Design Control• Design History File (DHF) maintenance• Final product Certificate of Analysis and approval for distribution (final product release)• Annual product review and field alerts
(b) (4)	<ul style="list-style-type: none">• Quality Control of incoming device components and sub-assemblies• Final product assembly, packaging and labelling• Device performance quality control testing• Maintenance of the Device Master Record and execution of Device History Records

- (b) (4)
- Quality Control of incoming device components
 - Assembly of the device components with the Drug Constituent Component to form the Cartridge Assembly
 - (b) (4)
 - (b) (4)

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

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

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

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

Inspection Recommendation:

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

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

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

MANUFACTURING



Addition of 2.0mg strength to NAI

As part of the implementation of the new NAI, 2.0 mg strength, changes to two modules were necessary:

(b) (4)

The following (b) (4) QSI documents describe the process validation activities associated with qualifying the changes to the (b) (4) updates to accommodate the NAI, 2.0 mg:

General Validation Plan / Assessments

- FPCL-MVP-0004-7 – Validation Master Plan for the kaleo Naloxone Auto-Injector NAI 0.4 mg, NAI-HD (lab code for NAI, 2.0mg) 2.0 mg, and (b) (4) 0.4 mg
- FPCL-SR-2015-0014-3 – NAI HD Impact Assessment

(b) (4)



PPQ Protocol

Per the discussion with the FDA in the pre-sNDA meeting (see Question 14 meeting minutes 23Dec2014), a PPQ protocol will be executed and a summary report of the PPQ will be approved before commercial distribution of the NAI, 2.0 mg. A copy of the PPQ protocol, FPCL-AVP-2016-0030 - Kaleo NAI-HD FAS PPQ Protocol is provided.

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

RECOMMENDATION

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

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

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

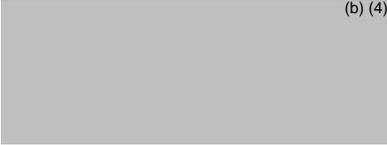
Prepared: RKang: 10/18/16
Reviewed: MKrueger: 10/19/2016

CTS No.: ICC1600357
sNDA-205787/S007

Review Cycle Meeting Attendance:
N/A

Inspectional Guidance

Firm to be inspected:



CDRH recommends the inspection under the applicable Medical Device Regulations.

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

REGULATORY STRATEGY

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

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

Primary Contact

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

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

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

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

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/s/

DIANA L WALKER
10/19/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: October 4, 2016

To: Diana Walker, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 205787/S-007
OPDP labeling comments for EVZIO (naloxone hydrochloride injection),
for intramuscular or subcutaneous use
Labeling Review

OPDP has reviewed the proposed package insert (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for EVZIO (naloxone hydrochloride injection), for intramuscular or subcutaneous use (Evezio) that was submitted for consult on June 14, 2016. Comments on the proposed PI are based on the version sent via email from Diana Walker (RPM) on September 20, 2016 entitled "sNDA 205787 S-007 proposed-uspi-tracked 20 sep16.docx" and the draft carton/container labeling submitted April 19, 2016.

OPDP has no comments on the proposed draft PI or the carton and container labeling at this time.

Please note that comments on the PPI and Instructions for Use will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

18 Page(s) of Draft Labeling have been Withheld in Full as
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/s/

LATOYA S TOOMBS
10/04/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 4, 2016

To: Sharon Hertz
Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

L. Shenee' Toombs, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name),
Dosage Form and
Route: EVZIO (naloxone hydrochloride injection), for intramuscular
or subcutaneous use

Application Type/Number,
Supplement/Number: NDA 205787/S-007

Applicant: kaleo, Inc.

1 INTRODUCTION

On April 19, 2016, kaleo, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) to their New Drug Application (NDA) 205787/S-007 for EVZIO (naloxone hydrochloride injection). This supplement proposes a new 2 mg strength Naloxone Auto-Injector.

EVZIO (naloxone hydrochloride injection) was originally approved on April 3, 2014 and is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on June 14, 2016 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for EVZIO (naloxone hydrochloride injection).

2 MATERIAL REVIEWED

- Draft EVZIO (naloxone hydrochloride injection) PPI received on April 19, 2016, and received by DMPP and OPDP on September 20, 2016.
- Draft EVZIO (naloxone hydrochloride injection) IFU received on April 19, 2016, and received by DMPP and OPDP on September 20, 2016.
- Draft EVZIO (naloxone hydrochloride injection) Trainer IFU received on April 19, 2016, and received by DMPP and OPDP on September 20, 2016.
- Draft EVZIO (naloxone hydrochloride injection) Prescribing Information (PI) received on April 19, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 20, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
10/04/2016

LATOYA S TOOMBS
10/04/2016

BARBARA A FULLER
10/04/2016

LASHAWN M GRIFFITHS
10/04/2016



**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date: September 26, 2016

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

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

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

Subject: Consult for NDA 205878/S007, ICC1600359

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

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

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

Digital Signature Concurrence Table	
Reviewer	John C. McMichael -S Date: 2016.09.29 07:45:09 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.09.29 08:09:15 -04'00'

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I. Purpose / Background

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

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

Question 6:

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

Agency Response:

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

Question 7:

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

Agency Response:

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

Question 10:

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

Agency Response:

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

Question 11:

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

Agency Response:

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

Discussion:

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

Question 12:

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

Agency Response:

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

[REDACTED]. 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.

Question 13:

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

Agency Response:

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

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

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

II. Administrative

Documents Reviewed:

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

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

CDRH Review Team:

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

III. Device Description and Performance Requirements

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

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

(b) (4)



The following information was taken from Auto-Injector – QS – Intelliject – IJ-200DI-O30 – NAI Product Requirements Specification, Document Number IJ-200DI-O30, Version 4, under 3.2.P.7 in GSR 0010.

Device Characteristic	Description / Specification
Injector Name	EVZIO or Naloxone Auto-Injector ('NAI')
Injector Platform Name	Intelliject
Priming Dose / Volume	N/A
Dose accuracy	± (b) (4) mL
Injection Time	(b) (4) Seconds
Injection Site	Outer thigh
Injection tissue and depth of injection	Intramuscular
Audible / visual feedback	NAI audible instructions output must support a minimum of (b) (4) SPL peak output measured at 0.5 meters directly in front of the device. Recorded voice instructions shall be used to

	<p>communicate the directions for use for the device.</p> <p>Visual indicators shall be utilized to aid in the communication of the directions for use for the device.</p> <p>Audible beeps/tones shall provide feedback to the user as to when the injection is complete.</p>
Cap Removal Force	The force to remove the safety guard and needle sheath shall be between (b) (4) pounds.
Activation Force	NAI needle shall be inserted at a minimum of (b) (4) of force.
Visibility of medication container	Yes
Last Dose Specifications and Safety Features	N/A
<p>Needle Specifications</p> <ul style="list-style-type: none"> • Length(s) • Gauge(s) • Connection type <ul style="list-style-type: none"> ○ ISO 11608-2:2012 ○ Prestaked 	<p>NAI needle shall have an exposed length range of (b) (4) " .</p> <p>(b) (4)</p>
Type of Use (e.g. single use, disposable, reusable, other)	Single Use, Disposable (emergency use)
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Adults
Injection mechanism (e.g., manual piston, spring, gas, etc.)	(b) (4)
Method of actuation	Force against injection site: The force to initiate plunger movement (initiation or break force) shall not exceed (b) (4) force. The Force to continue plunger movement (glide or sustaining force) shall not exceed (b) (4) force per ISO 11608-3.
Automated Functions	Injection, audible/visual feedback
Residual Medication	N/A
Delivered Volume (for single dose or selectable volume range for multidose pens)	(b) (4) mL (single dose)
Drug Container Type	Integrated cartridge
Dose Units of Measure (e.g., mL,	0.4 mg or 2.0 mg (subject of this supplement)

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

IV. Design Control Review

A. Design Review Summary

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

(b) (4) This supplement includes no changes to the design controls of the device constituent parts of the combination product, however due to the newly proposed dosage of 2 mg Naloxone, performance testing was required to re-verify the essential performance requirements of the device with the higher dosage form. It should be noted that the deliverable volume of the auto-injector remains the same for both dosage forms.

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

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

B. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	YES		Auto-Injector – QS – Intelliject – IJ-200DI-O30 – NAI Product Requirements Specification, 3.2.P.7 in GSR 0010
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	YES		Auto-injector – In Vitro Performance Testing – Appendix - Tables, 3.2.P.7 in GSR Sequence 0101
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	YES		Auto-injector – Risk Analyses, 3.2.P.7 in GSR 0010
Validation Data <ul style="list-style-type: none"> • Human factors • Clinical data 	YES		Human Factors information evaluated by OSE/DMEPA
	N/A		
Traceability Documentation	YES		N/A

*Sponsor may derive the regulatory requirements from 21 CFR 820.30 into multiple sets of documents. For example, injectors containing software may include separate software requirements and specification documents. In these circumstances, additional rows may need to be added to the table.

Reviewer Comment:

- (b) (4)
- A Phase I PK study in healthy volunteers was completed to compare the PK profiles of the approved 0.4 mg dose and the subject 2.0 mg dose.
- No new summative human factors studies evaluating the device-related efficacy were required to support the 2.0 mg dose as the design and user-interface are the same as the approved 0.4 mg dose Naloxone Auto-Injector. However, formative product label differentiation study was completed to evaluate if participants could tell the difference between the 0.4 mg and the 2.0 mg dose labels.

C. Design Verification and Validation Review

Summary of Design V&V Attributes:

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial?	X		
Selectable dose range on device matches the labeled dose range for the medication?	X		

Verification methods relevant to specific use conditions as described in design documents and labeling		X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			X	
Traceability demonstrated for specifications to performance data		X		
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	X		
	ISO 11608-2:2012 – Needles	X		
	ISO 11068-4:2006 – Electronic and Electromechanical Pen Injectors	X		
	ISO 11608-5:2012 – Automated Functions			
Adherence to FDA Guidance: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products		X		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry			X	
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	X		
	Sterility	X		
	Software / Cybersecurity			X
	Electrical Safety / EMC	X		
	Human Factors	X		

Reviewer Comment:

The reliability and essential performance requirements of the device after simulated shipping / transport is being requested as a PMR. Please see Section VIII for more details.

Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase III Study utilized the to-be-marketed device		NO	
Bioequivalence Study utilized to-be-marketed device	YES		
Simulated Actual Use Study utilized to-be-marketed device		NO	

Reviewer Comments:

- (b) (4)
- A Phase I PK study in healthy volunteers was completed to compare the PK profiles of the approved 0.4 mg dose and the subject 2.0 mg dose.
- No new summative human factors studies evaluating the device-related efficacy were required to support the 2.0 mg dose as the design and user-interface are the same as the approved 0.4 mg dose Naloxone Auto-Injector. However, formative product label differentiation study was completed to evaluate if participants could tell the difference between the 0.4 mg and the 2.0 mg dose labels.

Design Verification Review

The design verification review below is in the context of the information submitted in support of the 2 mg dosage that is the subject of Supplement 007.

Essential Performance Requirement	Specification	Verification for 2 mg Dose	Validation of Device	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Depth	Intramuscular	Auto-	Completed	YES – 6	NO	YES – under

		Injector – Shelf-life Stability and Expiration Dating	(b) (4)	months accelerated and 6 months real-time (long term)		original application
Injection Time	2 seconds for dispensing, 5 seconds for injection and full retraction into needle sheath	Auto-Injector – Shelf-life Stability and Expiration Dating		YES – 6 months accelerated and 6 months real-time (long term)	NO	YES – under original application
Dose Accuracy	(b) (4) mL	Auto-Injector – Shelf-life Stability and Expiration Dating		YES – 6 months accelerated and 6 months real-time (long term)	NO	YES – under original application
Visual/Audible Feedback	<p>One irreversible switch shall be used to indicate removal the safety guard.</p> <p>One switch shall be used to indicate when the injection has taken place.</p> <p>The green LED shall be used to draw attention to the safety guard.</p> <p>The green LED shall be used to draw attention to the needle injector area prior to injection.</p> <p>The red LED shall be used to indicate when the injection is complete.</p> <p>Recorded voice instructions</p>	Completed under original NDA – N/A for S007		N/A for S007	NO	N/A

	shall be used to communicate the directions for use for the device.					
Activation Force	(b) (4) lbs	Auto-Injector – Shelf-life Stability and Expiration Dating	(b) (4)	YES – 6 months accelerated and 6 months real-time (long term)	NO	YES – under original application
Needle Length	(b) (4) inches	Auto-Injector – Shelf-life Stability and Expiration Dating	(b) (4)	YES – 6 months accelerated and 6 months real-time (long term)	NO	YES – under original application
Needle Gauge	23 gauge	Completed under original NDA application - – N/A for S007	(b) (4)	N/A for S007	NO	N/A
Needle Connection Type	ISO 11608-2	Completed under original NDA application – N/A for S007	(b) (4)	N/A for S007	NO	N/A
Cap Removal Force	(b) (4) to remove cover (b) (4) to remove safety guard/needle sheath	Auto-Injector – Shelf-life Stability and Expiration Dating	(b) (4)	N/A for S007	NO	N/A

Reviewer Comments:

- The clinical acceptability of the above specifications was determined under the approval of the original NDA. There is a general Advisory Committee meeting scheduled for October 2016 to discuss issues surrounding minimum dosing requirements, etc. for Naloxone delivery combination products.
- The Shipping Study IJ-715R-03O was submitted by the Sponsor, however it included no testing of the essential performance requirements of the device constituent and only included acceptance criteria related to the packaging integrity. The reliability PMR laid out in Section VIII of this memo is intended to cover the functionality of the device after shipping/transport.

Below is the Stability Protocol taken from 3.2.P.8 of GSR Sequence 0080:

Table 3.2.P.8.1.3-5. Stability Protocol for NAI, 2.0 mg (b) (4) Registration Batches

Storage Conditions	Time Points								
	Initial	1	3	6	9	12	18	24	36
25 °C/60 %RH	A,B,C,D,E,F	B	B,E	B,C,D,E,F	B	B,C,D,E,F	B,E,F	B,C,D,E,F	B,C,D,E,F
30 °C/65 %RH				B		B,C,D,E			
40 °C/75 %RH		B	B,E	B,C,D,E					

A = Osmolality and Identification by HPLC

B = Solution Appearance, pH, and Assay and Related Substances by HPLC

C = Particulate Matter

D = Bacterial Endotoxin, Sterility

E = Activation Force, Volume Dispensed, Dispensing Time, Exposed Needle Length (will only be tested in Finished Product Batch F0119415BB)

Table 3.2.P.8.1.3-7. Stability Protocol for NAI, 2.0 mg Commercial Product

Storage Conditions	Time Points						
	Initial	6	9	12	18	24	36
25 °C/60 %RH	A,B,C,D,E	B	B	B,C,D,E	B	B,C,D,E	B,C,D,E

A = Osmolality and Identification by HPLC

B = Solution Appearance, pH, and Assay and Related Substances by HPLC

C = Particulate Matter

D = Bacterial Endotoxin, Sterility

E = Activation Force, Volume Dispensed, Dispensing Time, Exposed Needle Length

The Sponsor states that the proposed shelf-life of the combination product is 24 months (2 years).

The Sponsor has provided data from Batch F0119415BB referenced in Table 3.2.P.8.1.3-5: Stability Protocol for NAI, 2.0 mg (b) (4) Registration Batches in support of the maintenance of the essential performance requirements of the NAI with the proposed 2.0 mg dose.

The Sponsor was asked via information request to explain the difference between the Commercial Product referenced in Table 3.2.P.8.1.3-7 and the (b) (4) Registration Batch for which data was provided.

The Sponsor has completed 6 months of real-time long-term stability testing with the 2 mg dosage with results shown below:

Table 3.2.D.2.8.2-10: Device Performance Stability Data for Batch F0119415BB Stored at Long-Term Condition

Product:	NAI							
Lot:	F0119415BB							
Device Manufacturer	(b) (4)							
Manufacture Date								
Storage Condition:								
Initiation Date:								
Testing Facility:								
Table Notes:	Data reported as average ± standard deviation [minimum – maximum] mL = milliliter lb = pounds in = inches ms = millisecond NMT – Not more than NS – Not scheduled							
			Time Point					
Test	Stability Specification	Release	3 Months	6 Months	12 Months	18 Months	24 Months	36 Months
Activation Force			(b) (4)					
Volume Dispensed								
Dispensing Time ^a								
Exposed Needle Length								

^a Dispensing Time data displayed in milliseconds.

The Sponsor also completed 6 months accelerated aging stability testing at (b) (4) C to simulate 2 years of aging with the 2 mg dose and the results are shown below:

Table 3.2.D.2.8.2-11: Device Performance Stability Data for Batch F0119415BB Stored at Accelerated Stability Condition

Product:	NAI							
Lot:	F0119415BB							
Device Manufacturer	(b) (4)							
Manufacture Date								
Storage Condition:								
Initiation Date:								
Testing Facility:								
Table Notes:	Data reported as average ± standard deviation [minimum – maximum] mL = milliliter lb = pounds in = inches ms = millisecond NMT – Not more than NS – Not scheduled							
			Time Point					
Test	Stability Specification	Release	3 Months	6 Months				
Activation Force					(b) (4)			
Volume Dispensed								
Dispensing Time ^a								
Exposed Needle Length								

However, the following table taken from “Shelf-life Stability and Expiration Dating” of Sequence 0080 suggests that the accelerated aging was completed at (b) (4) degrees C as seen in the test results table above:

Accelerated Aging Study	Table 3.2.D.2.8.1-9	(b) (4)	
	Table 3.2.D.2.8.1-10		
(b) (4) Batch D01162A (3/30/15)	Table 3.2.D.2.8.1-11		
(b) (4) Lot F0119415BB (7/13/2015)	Table 3.2.D.2.8.1-12		

The Sponsor was asked via information request on 08/04/16 to explain this discrepancy in regards to 6 months of accelerated aging being equivalent to 2 years of real-time aging.

D. Risk Analysis

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

Summary of Risk Analysis

The Risk Analysis was evaluated under the original NDA approval of this combination product. The Sponsor provided the following high level description of the risk analysis and risk management activities completed for the auto-injector under Sequence 0010, 3.2.P.7:

The Risk Assessment for the NAI product is divided into five (5) categories as follows:

- (1) UFMEA: The User Failure Mode Effects Analysis (UFMEA) identifies the failure modes and associated risks with the use of NAI by the user and the use case scenarios during normal operation of NAI.
- (2) DFMEA: The Design Failure Mode Effects Analysis (DFMEA) for the design of NAI identifies risks associated with the specific components of the NAI.
- (3) Task Analysis with PCA: The Task Analysis with PCA (Perception, Cognition, Action analyses) identifies the failure modes and associated risks with the use of NAI by the user and the use case scenarios during normal operation of the NAI. The analysis utilizes human factors engineering best practice to determine potential use-related hazards associated with NAI.
- (4) PFMEA (semi-automated line): The Process Failure Mode Effects Analysis (PFMEA) identifies the failure modes and associated risks posed by the manufacturing process for NAI. This PFMEA is specific to the (b) (4) that supported engineering builds, pilot production, and clinical study batches for NAI. Refer to 3.2.D.2.12 Batch Analysis for the use and performance of the lots assembled using the (b) (4) line.
- (5) PFMEA (automated line): The Process Failure Mode Effects Analysis (PFMEA) identifies the failure modes and associated risks posed by the manufacturing process for the NAI at (b) (4). This PFMEA is specific to the automated line that supports commercial production for NAI.

The Sponsor provided a Component Design FMEA under the original NDA which established the potential failure modes of each component of the device constituent part of the combination product, the potential effects of the failures, the potential causes of the failures, the controls for the failures, and the verification of the controls for the potential failure modes. The DFMEA can be viewed in Document Number IJ-401RM-03O under Sequence 0010, Section 3.2.P.7.

The Risk Analysis was updated to reflect the extension of the butt-end of the needle that is described in the design change under the stability testing that was conducted to qualify the 2 mg dosage strength. An excerpt of the DFMEA is copied below to address the design change:

Row #	Assemblies	Design Output Component	Component Function	Potential Failure Mode
145		8-I Crimped Seal	Seal that gets crimped onto the cartridge that includes a septum that gets punctured by the needle during activation.	Doesn't allow needle to puncture completely
146				

Potential Effects of Failure	S e v	Potential Cause of Failure	O c c	Current Control/Detection Method*	D e t	R P N	Recommended Actions	Responsibility and Target Date	O c c	D e t	R P N
Slow Dispensing Time	2	Wrong Butt End Needle Spec or High Crimp Forces	7	Verification Testing	9	126	Update Butt end Needle Length for Needle Assembly to ensure complete puncture	10/30/2012	3	9	54

E. Labeling

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

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

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

(b) (4)

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

• Once the red safety guard is removed, EVZIO must be used immediately or disposed of properly. Do not attempt to replace the red safety guard once it is removed.

Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers (b) (4) naloxone hydrochloride injection, and retracts the needle fully into its housing. Post injection, the black base locks in place, a red indicator appears in the viewing window, and electronic visual and audible instructions signal that EVZIO has delivered the intended dose of naloxone hydrochloride and instructs the user to seek emergency medical attention.

Administration Instructions

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

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

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VII. Outstanding Deficiencies

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

VIII. Post-Market Commitments / Post-Market Requirements

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

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

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

IX. Recommendation

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

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/s/

DIANA L WALKER

10/14/2016

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



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

MEMORANDUM: PEDIATRIC REVIEW

From: Mona Khurana, M.D., Acting Pediatric Team Leader
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV

Through: John J. Alexander, M.D., M.P.H.
Deputy Director, DPMH

To: Division of Anesthesia, Analgesia, and Addiction Products

Drug Name: 2 mg Evzio Auto-Injector

Active Ingredient: Naloxone Hydrochloride

Therapeutic Class: Opioid Antagonist

Subject: Review of Pediatric Assessment

Sponsor: Kaleo, Inc.

Materials Reviewed

- March 2014 DPMH Memorandum under NDA 205787 (DARRTS Reference ID 3480223)
- Approval History of Evzio 0.4 mg Auto-Injector (accessed at Drugs@FDA September 8, 2016)
- Regulatory History of NDA 205787/S-007 and under IND 112292 in DARRTS
- Reviewer's Guide, Module 1.9 (Pediatric Correspondence), and Module 2.5 (Clinical Overview) in sNDA 205787/S-007

Consult Request

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted DPMH to evaluate the adequacy of the sponsor's pediatric assessment in supporting approval of a proposed

2 milligram (mg) auto-injector dose in the full pediatric age range. DAAAP is also requesting DPMH provide pediatric labeling recommendations.

I. Background

A. Approval History of New Drug Application (NDA) 205787

Evzio 0.4 mg Auto-Injector (NAI) was approved on April 3, 2014 in all ages for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and for immediate administration as emergency therapy in settings where opioids may be present.¹ This NDA was approved under the 505(b)(2) pathway on the basis of supportive data from the published literature and FDA's findings of safety and effectiveness for the previously approved Narcan for injection (NDA 016636).

Evzio is a single-injection, fixed-dose, auto-injector that is designed to deliver 0.4 mg of naloxone hydrochloride (HCl) intramuscularly (IM) or subcutaneously (SC) and was developed to facilitate administration of naloxone HCl by family members and caregivers (i.e., laypersons) in the non-healthcare setting. The unit incorporates both audio and visual instructions and cues to guide the person administering the drug during a medical emergency and is appropriate for administration by non-medically trained individuals. The total needle length is 5/8 of an inch, and 1/2 of an inch extends outside the device upon actuation.² The needle is fully retracted into the device housing after use.

Pediatric considerations during the review of NDA 205787 included adequacy of the proposed fixed 0.4 mg IM or SC dose in pediatric patients of all ages and local safety of both routes of administration in the youngest pediatric patients. While noting that a 0.4 mg fixed initial dose may be too low to be effective in some patients or situations, DPMH nevertheless stated the overall efficacy of the 0.4 mg fixed dose has been established and cited the following additional reasons as to why additional dosing data are not needed prior to pediatric approval: (1) naloxone's wide safety margin in pediatric patients; (2) existing approved labeling supporting a dose of 0.01 mg/kilogram (kg); (3) the need for an easily administered naloxone device; and (4) the product was to be packaged with two doses so a second dose would be readily available prior to the arrival of emergency medical services (EMS).³ Given the public health need for this product, consensus was reached between DPMH, DAAAP, and the Pediatric Review Committee

¹ Approval Letter for NDA 205787

(http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/205787Orig1s000ltr.pdf; accessed September 8, 2016)

² April 1, 2014 Cross Discipline Team Leader Memorandum under NDA 205787 (DARRTS Reference ID 3481785).

³ March 2014 DPMH Memorandum under NDA 205787 (DARRTS Reference ID 3480223)

(PeRC) that the product should be labeled for all pediatric ages as long as potential safety concerns in the youngest pediatric patients are adequately addressed in product labeling and evaluated in a post-marketing safety study. The PeRC agreed that approving NAI for use in all pediatric populations was reasonable but raised concerns that, in the youngest patients, the needle could strike bone, break off, and/or potentially not deliver the intended dose of a potentially life-saving drug. The PeRC further expressed concern that adequate delivery could be further compromised if the soft tissues of the thigh are compressed while delivering the drug.

At the time of approval, no Pediatric Research Equity Act (PREA)-mandated post-marketing study requirements were issued, but the following post-marketing safety study requirement was issued under the Food and Drug Administration Amendments Act (FDAAA) of 2007:⁴

2140-1 Conduct a study to demonstrate that the needle length is safe for use in patients less than one year of age during expected conditions of use.

Final Report Submission: 10/29/2014

The study protocol for PMR 2140-1 was reviewed under Investigational New Drug (IND) 112292 in consultation with DPMH and found to be acceptable to fulfill the PMR and consistent with the Centers for Disease Control recommendations for needle injections. DAAAP and DPMH reviewed the final study report submitted to FDA on October 29, 2014 (Study IJ-735E-030: “NAI Needle Integrity Testing”).^{5,6} In this study, the Evzio needle was injected into ham bone through a 4 inch skin pad to simulate injection into human bone. Twenty samples were tested at each of three locations (epiphysis, near the epiphyseal plate, and diaphysis), resulting in the testing of 60 total samples.

According to DAAAP’s review of the study, results demonstrated that damage occurs to the needle when injected into bone, as manifested by bent needle shafts and needle tips, with the worst damage occurring when the injection occurs into compact bone (e.g. diaphysis, near epiphyseal plate). However, the needle appeared to remain intact and the drug was delivered in all samples tested. Two samples injected into epiphysis showed slightly delayed retraction times

⁴ April 2011 Guidance for Industry Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act:
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm172001.pdf>;
accessed September 10, 2016.

⁵ July 7, 2015 DAAAP Medical Officer Review of PMR Study Report under NDA 205787 (DARRTS Reference ID 3788578).

⁶ January 26, 2015 DPMH Medical Officer Review of PMR Study report under NDA 205787 (DARRTS Reference ID 3690618).

of 5 seconds and 7 seconds, but DAAAP concluded the device continued to deliver naloxone in a reasonable timeframe even when retraction times were delayed. DAAAP noted that existing labeling language about pinching the thigh muscle in patients less than 1 year of age prior to Evzio administration should be retained to help reduce the likelihood of needle striking bone. DAAAP concluded that, although there were no instances of needle fragmentation, needle damage did occur and it would therefore be prudent to retain language in labeling that states the injection site should be inspected for residual needle parts, signs of infection, or both. DAAAP recommended continued routine post-marketing pharmacovigilance to monitor for adverse events related to any delays in drug delivery.

DPMH Comments: DPMH agrees with DAAAP's conclusion and recommendation to retain labeling language about inspecting the injection site for residual needle parts, signs of infection, or both.

DPMH did not recommend any additional labeling revisions based on the study results and did not recommend the need for any additional data to fulfil the PMR. Given the two reports of temporary drug flow restriction when bone impact blocked the needle opening, DPMH did recommend that DAAAP consider consulting the Center for Devices and Radiological Health if there are continued concerns about temporary drug flow restriction or if post-marketing adverse events related to delays in drug delivery are reported.

B. Regulatory History of Supplemental NDA 205787/S-007

The sponsor submitted a Prior Approval Supplement (PAS) on April 19, 2016 to seek approval of a new 2 mg strength Naloxone Auto-Injector (NAI-HD) for the same indications as currently approved for Evzio. The sNDA is supported by a pivotal dose proportionality study in 24 healthy adults, 24 to 54 years of age, comparing the 2 mg NAI-HD dose with the 0.4 mg Evzio dose. The sponsor also conducted a product label differentiation study in 33 participants to determine users' ability to visually identify and successfully differentiate between the 0.4 mg Evzio and the proposed 2 mg NAI-HD devices and cartons. FDA did not require additional human factors studies to evaluate device-related efficacy for NAI-HD.

NAI-HD is a drug-device combination product consisting of a single-use auto-injector which delivers a 2 mg naloxone dose via IM or SC injection. The formulation and dosing volume are identical to that of Evzio, but the NAI-HD product contains a higher naloxone HCl concentration (2 mg/0.4 milliliters [mL]) compared to Evzio (0.4 mg/0.4 mL). The needle specifications of the NAI and NAI-HD are identical. The exposed needle length for NAI-HD ranges from [REDACTED] (b) (4) inches.⁷

⁷ Module 3.2.P.5 of NDA 205787/S-007 submission

At a pre-sNDA meeting, FDA advised the sponsor to submit a review and analysis of the published literature, leveraging existing pediatric information in approved labeling for their reference product, to evaluate the safety and effectiveness of the 2 mg dose of NAI-HD in all pediatric populations, similar to what the sponsor did to support pediatric labeling for Evzio 0.4 mg Auto-Injector.⁸ FDA recommended including these data with the sNDA submission. An Agreed Initial Pediatric Study Plan (iPSP) containing this information was included in the sNDA submission.⁹

The Agreed iPSP includes a tabular summary comparing naloxone exposure based on the fixed-dose administration of Evzio to NAI-HD in pediatric patients weighing 4.1 kg to 95.2 kg. See Appendix A. According to the sponsor, this information shows that administration of a fixed 2 mg dose via the NAI-HD is consistent with pediatric dosing recommended in approved naloxone HCl labeling and recommended by the American Academy of Pediatrics for all patients weighing more than 20 kg but is higher than both approved labeling and AAP dosing recommendations for patients weighing less than 20 kg. A 2 mg dose of NAI-HD will provide a 0.49 mg/kg naloxone dose to patients weighing 4.1 kg.

DPMH Comments: The sponsor's table does not account for pediatric patients down to birth and whose weight is more than two standard deviations from the mean for age. If the proposed product is approved for use in all pediatric ages from birth to less than 17 years, then administration of a fixed 2 mg dose would result in the delivery of approximately 1 mg/kg naloxone to a newborn at the 5th percentile for weight and 0.7 mg/kg naloxone to a newborn at the 95th percentile for weight.¹⁰ These doses are 7 to 10 times higher than the initial naloxone dose recommended by the American Academy of Pediatrics' (AAP) Committee on Drugs (COD).¹¹ The AAP COD recommends a parenteral naloxone dose of 0.1 mg/kg for pediatric patients from birth to age 5 years or 20 kg of body weight and a dose of 2 mg for pediatric patients older than age 5 years or weighing more than 20 kg. Administration of the fixed 2 mg dose to a 16 year old at the 5th and 95th percentiles for weight would result in the delivery of 0.04

⁸ December 23, 2014 Meeting Minutes for Type B Pre-sNDA Meeting under IND 112292 (DARRTS Reference ID 3677802)

⁹ Agreement Letter issued to the sponsor on October 16, 2015 under IND 112292 (DARRTS Reference ID 3834210)

¹⁰ Centers for Disease Control and Prevention Clinical Growth Charts for Children Birth to 24 Months: http://www.cdc.gov/growthcharts/who_charts.htm#The WHO Growth Charts; accessed September 10, 2016.

¹¹ Committee on Drugs Naloxone Dosage and Route of Administration for Infants and Children: Addendum to Emergency Drug Doses for Infants and Children. *Pediatrics* 86(3): 484-485, 1990.

mg/kg and 0.02 mg/kg naloxone, respectively.¹² These doses are less than the AAP recommended initial naloxone doses but higher than approved pediatric doses in Narcan labeling.

II. Pediatric Assessment

To support pediatric approval of NAI-HD, the sponsor re-evaluated the literature with a focus on the safety of naloxone at doses greater than 0.1 mg/kg, at fixed doses greater than 0.4 mg per dose, or both in pediatric patients. The sponsor identified six publications consisting of the following: (1) two case reports of accidental opioid ingestion in pediatric patients;^{13,14} (2) a case series describing accidental buprenorphine exposure in pediatric patients;¹⁵ (3) a retrospective case review describing symptomatic accidental buprenorphine exposure in pediatric patients;¹⁶ (4) a review article on the management of opioid overdose;¹⁷ and (5) a randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of naloxone in asphyxiated newborns.¹⁸

One case report described a 2 year old boy weighing 12.5 kg who became apneic with central nervous system (CNS) depression after oral exposure to 50 mg of nor-methadone due to a pharmacy dispensing error.¹³ He immediately improved after receiving an initial IV naloxone dose of 0.008 mg/kg but had recurrent CNS depression 1 to 2 hours later, requiring additional IV naloxone at higher doses. Administration of each subsequent naloxone dose reversed his narcosis but, because he deteriorated each time 30 to 60 minutes post-dosing, he was placed on a naloxone infusion at 0.024 mg/kg/hour for 10.3 hours. He received a total of 0.56 mg/kg

¹² Centers for Disease Control and Prevention Clinical Growth Charts for Children 2 to 20 Years: http://www.cdc.gov/growthcharts/clinical_charts.htm; accessed September 10, 2016.

¹³ Gourlay GK and Coulthard K. The Role of Naloxone Infusions in the Treatment of Overdoses of Long Half-Life Narcotic Agonists: Application to Nor-Methadone. *British Journal of Clinical Pharmacology* 15: 269-272, 1983.

¹⁴ Romac D. Safety of Prolonged, High-Dose Infusion of Naloxone Hydrochloride for Severe Methadone Overdose. *Clinical Pharmacology* 5: 251-254, 1986.

¹⁵ Geib AG, Babu K, Ewald MB, et al. Adverse Effects in Children after Unintentional Buprenorphine Exposure. *Pediatrics* 118: 1746-1751, 2006.

¹⁶ Pedapati EV and Bateman ST. Toddlers Requiring Pediatric Intensive Care Unit Admission Following At-Home Exposure to Buprenorphine/Naloxone. *Pediatric Critical Care Medicine* 12(2): e102-e107, 2011.

¹⁷ Boyer EW. Management of Opioid Analgesic Overdose *New England Journal of Medicine* 367(2): 146-155, 2012.

¹⁸ Chernick V, Manfreda J, De Booy V, et al. Clinical Trial of Naloxone in Birth Asphyxia. *Fetal and Neonatal Medicine Journal of Pediatrics* 113: 519-525, 1988.

naloxone over 28 hours. He recovered uneventfully without sequelae and was discharged 3 days after hospitalization. No naloxone-related adverse events were reported.

The other case report described a 13 year old girl who was found unconscious with labored breathing after ingesting approximately 200-300 mg methadone HCl.¹⁴ She received naloxone 0.4 mg IV by EMS with increased level of consciousness and increased respiratory rate, but required three additional doses of 0.4 mg IV naloxone on the way to the emergency room (ER) due to recurring episodes of unresponsiveness. Her blood methadone concentration in the ER was 0.9 mg/liter (L); a blood concentration of 1.6 mg/L has been reported to be lethal. She required 3 additional 0.4 mg IV naloxone boluses in the ER before admission. Due to persistent periods of apnea upon admission, she was started on a continuous naloxone infusion at an initial rate of 0.006 mg/kg/hour that was titrated up to a maximum rate of 0.018 mg/kg/hour. She required a continuous naloxone infusion for a total of 65.5 hours during which time she received a cumulative dose of 0.65 mg/kg. No naloxone-related adverse events were reported.

The case series described five children less than 2 years of age with accidental ingestion of combination tablets containing buprenorphine and naloxone.¹⁵ Four of the 5 children were treated with IV naloxone at weight-based doses; one child received close to the labeled initial dose of 0.01 mg/kg (0.016 mg/kg) while the other 3 children received close to the AAP recommended higher initial weight-based dose of 0.1 mg/kg (0.072 mg/kg, 0.08 mg/kg, and 0.1 mg/kg). All 4 children improved with administration of the naloxone dose but required more than one naloxone IV bolus dose due to recurrence of respiratory depression, CNS depression, or both. The child given the initial starting dose of 0.072 mg/kg subsequently required an IV infusion due to recurrent lethargy at a rate of 0.045 mg/kg/hour for 17 hours. All 4 children who received naloxone had reversal of their respiratory depression and recovered uneventfully. No naloxone-related adverse events were reported.

The retrospective case review aimed to determine the prevalence of symptomatic buprenorphine exposure requiring pediatric intensive care unit admission in pediatric patients less than 3 years of age at a single academic center from 2007 to 2009, the severity of the associated toxicity, and what clinical interventions were effective.¹⁶ Nine cases of opioid toxicity, most commonly presenting with drowsiness or lethargy, were identified involving single-agent exposure to the combination product buprenorphine/naloxone at the child's primary residence. In all 9 cases, an orange residual liquid or a partial pill suggestive of the sublingual formulation was found, suggesting the drug had dissolved in the child's mouth instead of being swallowed. The median (range) age was 22 months (10 months to 33 months). Six patients received IV or IM naloxone at a mean (range) dose of 0.07 mg/kg (0.03 mg/kg to 0.1 mg/kg); 2 patients received their 1st dose by EMS pre-hospital and 4 patients received their first dose in the ER. One patient received an initial IV dose of 0.09 mg/kg and was then placed on an IV infusion at 0.05 mg/kg/hour for 16 hours; the infusion was started because the initial IV bolus dose did not sufficiently reverse the

respiratory effects of opioid exposure. The AAP recommended naloxone dose of 0.1 mg/kg was used in 3 cases. In the other 6 cases, smaller doses were effective at reversing symptoms. Naloxone administration was associated with marked clinical improvement in all cases. No naloxone-related adverse events were reported.

The randomized, double-blind, placebo-controlled trial was conducted in 193 newborns with low one minute Apgar scores due to intrauterine asphyxia who received 0.4 mg/kg IM naloxone or normal saline.¹⁸ Naloxone administration did not have a significant effect on spontaneous respiratory frequency or heart rate up to 30 minutes after injection or at 24 hours of age. Increased muscle tone of the upper and lower extremities was associated with naloxone use, which the authors opined was not desirable in the context of inadequate oxygen delivery to vital organs. The authors concluded that naloxone has no readily apparent benefit in the resuscitation of the asphyxiated newborn.

DPMH Comments: This trial was conducted exclusively in asphyxiated newborns, and newborns whose mothers had been given an opioid analgesic within four hours of delivery were excluded. Therefore, the safety findings are not necessarily generalizable to the population for whom NAI-HD would be indicated.

Overall, these publications support concerns that a single, low initial naloxone dose may be inadequate to provide continuous antagonism of opioid effects in some settings and that repeated doses of naloxone are necessary to achieve and sustain opioid reversal in cases of exposure to long-acting opioids, large opioid ingestions, or both.

Rare cases of adverse reactions to high doses of naloxone have been described primarily in post-surgical adult patients that consist of hypertension, arrhythmias, cardiac arrest, and gastrointestinal disturbances and are currently captured in product labeling. None of the six publications included in this pediatric assessment described naloxone-related adverse events in pediatric patients at administered cumulative doses of up to nearly 0.8 mg/kg.

These publications provide further evidence that precipitation of acute opioid withdrawal is unlikely to occur with use of NAI-HD in the intended pediatric population since the most likely cause of opioid exposure in younger pediatric patients, particularly those less than 6 years of age, is acute accidental opioid ingestion.^{19,20} However, administration of the 2 mg fixed dose via the NAI-HD in opioid-dependent pediatric patients, including neonates, may result in an abrupt

¹⁹ Martin TC and Rocque M. Accidental and Non-Accidental Ingestion of Methadone and Buprenorphine in Childhood: A Single Center Experience, 1999-2009. *Current Drug Safety* 6: 12-16, 2011.

²⁰ Hayes BD, Klein-Schwartz W, and Doyon S. Toxicity of Buprenorphine Overdoses in Children. *Pediatrics* 121(4): e782-e786, 2008.

and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. Neonatal opioid withdrawal syndrome (NOWs), unlike opioid withdrawal syndrome in adults, may be life-threatening.

III. Conclusions

The pediatric assessment supports the utility of the higher fixed naloxone dose provided by NAI-HD to achieve and sustain opioid reversal, particularly in cases of pediatric exposure to long-acting opioids, large opioid ingestions, or both. The pediatric assessment also suggests that pediatric patients with acute opioid exposure may safely receive naloxone at cumulative doses of up to nearly 0.8 mg/kg. The assessment provides further evidence that precipitation of acute opioid withdrawal is unlikely to occur with use of NAI-HD in the majority of the intended pediatric population since the most likely cause of opioid exposure in younger pediatric patients, particularly those less than 6 years of age, is acute accidental opioid ingestion. However, administration of the 2 mg fixed dose via the NAI-HD in the subset of opioid-dependent pediatric patients, including neonates, may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome which can be life-threatening in neonates.

The proposed 2 mg fixed dose may be most appropriate for use by lay people in the community and other non-medically supervised settings where the goal would be rapid reversal of opioid effects due to acute accidental or intentional ingestion with less concern about precipitating acute withdrawal symptoms. Such settings are likely to have limited to no other treatment alternatives available. Therefore, precipitation of acute withdrawal symptoms would be preferable to the potentially life-threatening consequences of prolonged respiratory depression and hypoxia due to opioid overdose.

Use of the NAI-HD is less desirable when careful dose-titration rather than fixed dose-administration is needed by healthcare professionals in certain supervised medical settings such as post-operative recovery rooms and delivery rooms to avoid the consequences of abrupt reversal of chronic opioid effects. In these settings where slower, incremental reversal of opioid effects are needed as an adjunct to assisted ventilation and other supportive resuscitative measures, use of a naloxone-containing product that can be titrated to effect and dosed according to weight rather than as a large, fixed dose may be preferable and should be recommended.

IV. Recommendations

DPMH recommends approval of NAI-HD for the proposed indications in pediatric patients of all ages. Product labeling should capture the following:

- Safety concerns about precipitating acute withdrawal if this product is used in pediatric patients with chronic opioid exposure
- Convey the importance of using other naloxone products which can be dosed by weight, rather than NAI-HD, in supervised healthcare settings when careful dose-titration is needed
- Consistently state product may be re-administered for recurrent respiratory depression, CNS depression, or both; the proposed labeling currently only includes respiratory depression

DPMH recommends the following labeling revisions (suggested text added in bold italics and suggested deletions as strikethrough):

1 INDICATIONS AND USAGE

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 *in adults and pediatric patients*.

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.

EVZIO is not a substitute for emergency medical care.

2.2 Dosing Information

Dosing in Adults and Pediatric Patients over Age One *Year*

Instruct patients or their caregivers to administer EVZIO according to the Instructions for Use, intramuscularly or subcutaneously.

Dosing in Pediatric Patients under Age One *Year*

In pediatric patients under the age of one *year*, the caregiver should pinch the thigh muscle while administering EVZIO. *Carefully observe the administration site for* (b) (4) *signs of infection* (b) (4)

5.3 Precipitation of Severe Opioid Withdrawal

The use of EVZIO in patients who are opioid dependent may precipitate an acute abstinence syndromeopioid withdrawal characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or

vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. **Unlike opioid withdrawal in adults, opioid withdrawal in neonates** ~~In neonates, opioid withdrawal~~ **manifesting as seizures** may be life-threatening if not recognized and properly treated. **Other** ~~and may include the following~~ signs and symptoms **in neonates include:** convulsions, excessive crying and hyperactive reflexes. **Monitor patients for the development of the signs and symptoms of opioid withdrawal.**

(b) (4)

8.4 Pediatric Use

The safety and effectiveness of EVZIO (for intramuscular and subcutaneous use) have been established in pediatric patients **of all ages** for (b) (4)

(b) (4) Use of naloxone hydrochloride in **all** pediatric patients is supported by **the safe and effective use of another naloxone hydrochloride injectable product. No pediatric studies were conducted for EVZIO.** (b) (4)

(b) (4)

Absorption of naloxone hydrochloride following subcutaneous or intramuscular administration in pediatric patients may be erratic or delayed. Even when the opiate-intoxicated pediatric patient responds (b) (4) appropriately to naloxone hydrochloride injection, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

In opioid-dependent pediatric patients, (including neonates), administration of naloxone **hydrochloride** may result in an abrupt and complete reversal of opioid effects, precipitating an acute opioid withdrawal syndrome. **There may be clinical settings, particularly the postpartum period in neonates with known or suspected exposure to maternal opioid use, where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms. Unlike acute opioid withdrawal in adults, acute opioid withdrawal in neonates manifesting as seizures may be life-threatening if not recognized and properly treated. Other signs and symptoms in neonates may include excessive crying and hyperactive reflexes. In these settings where it may**

be preferable to avoid the abrupt precipitation of acute opioid withdrawal symptoms, consider use of an alternative, naloxone product which can dosed according to weight and titrated to effect. [see Contraindications (5.3)].

In pediatric patients under the age of one year, the caregiver should pinch the thigh muscle while administering EVZIO. Carefully observe the administration site for evidence of residual needle parts, signs of infection, or both. [see Dosing Information (2.2)].

(b) (4)

(b) (4)

Appendix A**Naloxone Exposure Based on Fixed-Dose Administration of Evzio and NAI-HD**

Weight (lbs)	Weight (kg)	EVZIO Dose (mg/kg)	2x EVZIO Dose (mg/kg)	05A Dose (mg/kg)	2x 05A Dose (mg/kg)
9	4.1	0.10	0.20	0.49	0.98
10	4.5	0.09	0.18	0.44	0.89
20	9.1	0.04	0.09	0.22	0.44
30	13.6	0.03	0.06	0.15	0.29
40	18.1	0.02	0.04	0.11	0.22
44.1	20	0.02	0.04	0.10	0.20
50	22.7	0.02	0.04	0.09	0.18
60	27.2	0.01	0.03	0.07	0.15
70	31.8	0.01	0.03	0.06	0.13
80	36.3	0.01	0.02	0.06	0.11
90	40.8	0.01	0.02	0.05	0.10
100	45.4	0.01	0.02	0.04	0.09
110	49.9	0.01	0.02	0.04	0.08
120	54.4	0.01	0.01	0.04	0.07
130	59	0.01	0.01	0.03	0.07
140	63.5	0.01	0.01	0.03	0.06
150	68	0.01	0.01	0.03	0.06
160	72.6	0.01	0.01	0.03	0.06
170	77.1	0.01	0.01	0.03	0.05
180	81.6	0.005	0.01	0.02	0.05
190	86.2	0.005	0.01	0.02	0.05
200	90.7	0.004	0.01	0.02	0.04
210	95.2	0.004	0.01	0.02	0.04

(Source: Table 2 on page 14 of Agreed iPSP included in Module 1.9 of sNDA 205787/S-007 submission)

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/s/

MONA K KHURANA
09/22/2016

JOHN J ALEXANDER
09/23/2016

PRODUCT LABEL DIFFERENTIATION STUDY REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: September 22, 2016

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 205787/S-007

Product Name and Strength: Evzio, (naloxone HCl injection),
0.4 mg (1 mg/mL)
Proposed: 2 mg

Product Type: Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Kaleo, Inc.

Submission Date: April 19, 2016

OSE RCM #: 2016-940

DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

DMEPA Associate Director for Human Factors: Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

On April 3, 2014, DAAAP approved the original naloxone auto-injector (NAI), Evzio 0.4 mg, under NDA 205787. Evzio was developed to facilitate administration of naloxone hydrochloride by family members and caregivers (i.e. laypersons) in the non-healthcare setting. Kaleo Inc. submitted an efficacy supplement (S-07) to seek approval of a new higher 2 mg strength NAI (NAI, 2mg or NAI-HD). Thus, the DAAAP requested DMEPA evaluate the Applicant's proposed updated full prescribing information (FPI), instructions for use (IFU), carton labeling, outer case, and device labels for the 2 mg strength, and a label differentiation study.

1.1 REGULATORY BACKGROUND

On June 29, 2015, the Sponsor submitted questions responding to DMEPA's previous comments provided during a pre-NDA meeting on December 8, 2014 regarding device label and case and carton labeling design to differentiate the currently approved Evzio (naloxone HCl injection) 0.4 mg Auto-Injector from the proposed 2 mg strength (Appendix F). Subsequently, the Sponsor proposed changes to the container labels and carton labeling for both strengths. The Sponsor also conducted a risk analysis to evaluate the risk for product selection errors between the two strengths. On July 28, 2015, DMEPA requested the Sponsor to further consider product selection errors due to negative transfer in their risk analysis due the similarity in color scheme for both strengths (Appendix F).

Evzio is currently marketed as a 0.4 mg NAI. Kaleo, Inc is proposing a new higher strength 2 mg NAI. Within the submission (b) (4)

Kaleo responded on July 28, 2016 with the following, (b) (4)

- EVZIO 0.4 mg (b) (4)
 -
 -
 -
- EVZIO (b) (4)
 -
 -

¹ Walker, D. sNDA Information Request, July 25, 2016.

In addition, we performed a risk assessment of the proposed updated full prescribing information (FPI), instructions for use (IFU), carton labeling, outer case, and device labels for the 2 mg strength.

We also reviewed the Sponsor's report for a label differentiation study to determine whether the product user interface can support correct product selection.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The following sections outline our review of the product labeling including FPI, carton label/carton labeling, IFU, and the labeling differentiation study.

Full Prescribing Information (FPI)

We note the FPI Dosage and Administration, Dosage Forms and Strengths, and Storage and Handling Sections have been updated to reflect the new strength. However, Dosage Forms and Strengths section within the Highlights section has not been updated to include the new 2 mg strength. Also of note, the 2 mg strength is expressed as "2.0" throughout the FPI. The use of terminal zeros can lead to tenfold dosing errors when the decimal point goes unseen (e.g., 2.0

mL is seen as 20 mL).² We provide recommendations to address the identified deficiencies in Section 4.1 below.

Of note, the Dosage and Administration section does not currently specify under what circumstances each strength should be used. As stated by the Medical Officer in an email dated July 28, 2016, we do not currently have data to support the use or provide guidance as to when to choose one dose over another.

Container Label and Carton Labeling

Kaleo submitted carton labeling and container labels for the proposed 2 mg strength for review. The carton labeling and container label are identical to the marketed 0.4 mg strength with the exception of a different color scheme to help mitigate product selection errors.

Of note, the 2 mg strength is expressed as “2.0” on both the label and labeling. The use of terminal zeros can lead to tenfold dosing errors when the decimal point goes unseen (e.g., 2.0 mL is seen as 20 mL).³ We provide recommendations to address the identified deficiencies in Section 4.2 below.

IFU (Trainer and Auto-injector)

 (b) (4)
to help caregivers to be able to differentiate between each in addition to verbal descriptions. Of note, the 2 mg strength is expressed as “2.0” within the IFU. The use of terminal zeros can lead to tenfold dosing errors when the decimal point goes unseen (e.g., 2.0 mL is seen as 20 mL).² We provide recommendations to address the identified deficiencies in Section 4.2 below

Label Differentiation Study

Kaleo, Inc. also performed a labeling differentiation study to evaluate if participants can successfully differentiate between the 0.4 mg NAI Evzio and the proposed 2 mg NAI Evzio auto-injectors and cartons. Participants (n=33) representing laypeople, pharmacists, and pharmacy technicians were given two tasks. Within this study, participants were asked to retrieve one of the two dose strengths (i.e. 0.4 mg or 2 mg) during each task. The study was designed such that half of the lay user participants were assigned to one dose strength (either a 0.4 mg or 2 mg), and the other half of the participants were assigned to the other dose strength. Once assigned, the lay users were introduced to the carton and auto-injector for that specific strength during for an exploration period. After the exploration period they were then asked to retrieve that specific dose strength that they were assigned. After participants completed each task and

² ISMP—2014-15 Targeted Medication Safety Best Practices for Hospitals. Accessed April 2015 at <http://www.ismp.org/tools/bestpractices/TMSBP-for-Hospitals.pdf>.

³ ISMP—2014-15 Targeted Medication Safety Best Practices for Hospitals. Accessed April 2015 at <http://www.ismp.org/tools/bestpractices/TMSBP-for-Hospitals.pdf>.

after completing all tasks, the test administrator asked open-ended task-specific questions to gather information about how participants differentiated between products.

We noted three issues related to the study methodology to evaluate the lay user participants:

1. The study allowed participants time to “explore” the product, which in a worst case scenario may not occur in actual use.
2. The study did not incorporate a realistic decay period follow the exploration period. In actual use, we expect there is a period that may elapse between receiving the product and using the product.
3. The participants were assigned and introduced to only one of the two dose strengths. The subsequent differentiation task was focused on the participants’ ability to recall and select the dose strength that they were previously introduced to rather than including a simulated emergency scenario in which they would be faced with the two available dose strengths, and would need to identify and select the correct strength.

While the noted issues indicate that the study was not a true label differentiation study, we focused our review on the information that the participants provided in terms of subjective feedback on what helped them identifying the correct product.

The study results showed that all participants selected the correct carton off the shelf according to the carton they were introduced to at the beginning of the task. However for the task of selecting the auto-injector, one layperson selected both auto-injectors (the 0.4 mg and 2 mg dose strength) rather than selecting the correct auto-injector (2 mg) specified in the differentiation task. Root cause analysis by the participant indicated that she selected both auto-injectors (0.4 mg and 2 mg) because she recalled seeing two auto-injectors in the pharmacy bag during the exploration period, which in fact contained two auto-injectors of the same strength (2 mg). Upon further debrief, she indicated that she focused mostly on the auto-injector’s blue color during the exploration period and inaccurately recalled seeing a yellow auto-injector during the exploration period. In the previous task she did select the correct carton (i.e. 2 mg Evzio carton). Per Kaleo, Inc., the residual risk associated with this use error was acceptable. We agree with the sponsor’s determination and do not have any additional recommendations at this time.

Other participants were asked during the debrief period to identify the characteristics of the Evzio carton that helped them the most to identify the product correctly. The color scheme of the carton and auto-injector were utilized by the majority of the study participants. The dose strength printed near the top of the carton on the principal display panel (PDP) was utilized by all but one participant in the pharmacist and pharmacy technician group. The participants also noted the solid red or white bubble surrounding the dose strength on the revised cartons drew their attention to the dose strength. Given the subjective feedback from participants, we found the proposed color scheme of the 2 mg product acceptable, and that the two available strengths that can co-exist on the market (b) (4)
 and help to reduce product selection errors. We will monitor postmarket for any confusion or product selection errors regarding this product.

FAERS cases

DMEPA conducted a FAERS search for the currently marketed product and determined that the retrieved cases do not inform our review of the proposed labels and labeling (see Appendix E).

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the proposed FPI, IFU, container labels, and carton labeling are acceptable from a medication error perspective. Also, DMEPA finds the differentiation study results acceptable. The subjective feedback from the study participants indicate that the participants utilized the new proposed color scheme to help differentiate between products in the label differentiation study. However, to include important information and to prevent possible dosing errors, we provide recommendations in Section 4.1 and 4.2, respectively. We advise that these recommendations should be implemented prior to approval of this application.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. FPI

1. Remove all terminal zeroes from the FPI and replace with whole numbers (2 mg instead of 2.0 mg) to prevent tenfold dosing errors.²
2. Highlights Section, Dosage Forms and Strengths: add the 2 mg dosage form and strength to the section

4.2 RECOMMENDATIONS FOR KALEO, INC

We recommend the following be implemented prior to approval of this NDA Supplement:

A. All Carton labeling, container labels, and IFU's

1. Remove all terminal zeroes from the FPI and replace with whole numbers (2 mg instead of 2.0 mg) to prevent tenfold dosing errors.²

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Evzio that Kaleo, Inc. submitted on April 19, 2016.

Table 2. Relevant Product Information for Evzio	
Initial Approval Date	April 3, 2014
Active Ingredient	naloxone hydrochloride
Indication	The emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. The requirement for repeat doses of EVZIO depends upon the amount, type, and route of administration of the opioid being antagonized.
Route of Administration	Intramuscular and subcutaneous
Dosage Form	Injection
Strength	0.4 mg (1 mg/ml) Proposed: 2 mg
Dose and Frequency	Administer the initial dose of EVZIO to adult or pediatric patients intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and seek emergency medical assistance.
How Supplied	Carton containing two EVZIO (naloxone hydrochloride injection, USP) 0.4 mg auto-injectors and a single Trainer for EVZIO Proposed: Carton containing two EVZIO (naloxone hydrochloride injection, USP) 2.0 mg auto-injectors and a single Trainer for EVZIO
Storage	15°C to 25°C (59°F to 77°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 5, 2014, we searched the L:drive and AIMS using the terms, Evzio to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified five previous reviews^{4,5,6,7,8}, and we confirmed that our previous recommendations were implemented.

⁴ Borders-Hemphill, V. Label and Labeling Review for Evzio (naloxone hydrochloride) NDA 205787. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 03 27. RCM No.: 2012-2402.

⁵ Borders-Hemphill, V. Label and Labeling Review for Evzio (naloxone hydrochloride) NDA 205787. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 02 02. RCM No.: 2012-2402.

⁶ Borders-Hemphill, V. Label and Labeling Review for naloxone hydrochloride (NDA 205787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 12 11. RCM No.: 2012-2402.

⁷ Borders-Hemphill, V. Human Factors Study Protocol Review Memo for naloxone hydrochloride (PIND 112292). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 01 09. RCM No.: 2012-2402.

⁸ Baugh, D. Human Factors Study Protocol Review for naloxone hydrochloride (PIND 112292). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 04 30. RCM No.: 2012-686.

APPENDIX C. LABEL DIFFERENTIATION STUDY RESULTS

C.1 Background

The naloxone autoinjector (NAI) Human Factors Engineering (HFE) development program was supported [REDACTED] ^{(b) (4)} and also included an NAI Formative User Needs Study (IJ-1000FE-03O), an NAI Formative Usability and Label Evaluation Study (IJ-1001FE-03O) and an NAI Summative Design Validation Study of the User Interface (IJ-1025SE-03O), designed as a “worst case” user scenario in which no prior training was provided. These studies were submitted with the initial NDA submission for approval of 0.4 mg NAI.

No new summative Human Factors studies were required to support the 2 mg NAI program; however, a formative product label differentiation study was conducted.

C.2 Label Differentiation Study Results

Study Design and Objectives

Product label differentiation study objective was to evaluate if participants can successfully differentiate between the 0.4 mg NAI Evzio and the proposed 2 mg NAI Evzio devices and cartons. A product selection error risk analysis was performed and objective and subjective data was collected to evaluate the selection task.

Study Participants

33 Participants

- lay people (n=6)
 - ages 27-52
 - 1 had prior auto-injector (Epipen) experience
 - Visual impairments included glasses, distance; glasses, reading; glasses, reading and distance; contact lenses
- pharmacists (n=16)
 - ages 29-66
 - all had experience dispensing injection devices
 - Visual impairments included glasses, distance; glasses, reading; glasses, reading and distance; glaucoma suspect
- pharmacy technicians (n=11)
 - ages 20-54
 - all had experience dispensing injection devices
 - Visual impairments included glasses, distance; glasses, reading; glasses, reading and distance

Test Activities

Three tasks were performed:

- 1) Carton retrieval (all user groups)

- 2) Auto-injector retrieval (laypeople only)
- 3) Carton retrieval (pharmacists and pharmacy technicians only)

Participants were asked to retrieve one of the two dose strengths during each task. The test team counterbalanced the specified dose strength between participants such that half of the participants were asked to select the 0.4 mg strength and half were asked to select the 2 mg strength.

Laypeople were given an opportunity to explore the carton and auto-injector prior to administering Task I. Specifically, the participant was provided with the carton and 2 of the same auto-injector they were later asked to select during Task 1 and Task 2, respectively. After participants completed each task and after completing all tasks, the test administrator asked task-specific questions.

APPENDIX D: RISK ANALYSIS FOR EVZIO 0.4 MG AND 2.0 MG PRODUCT SELECTION ERRORS⁴

Risk	Potential Cause	Possible Outcome, Probability & Severity	Planned Mitigation
Patient receives EVZIO 0.4 mg instead of EVZIO 2.0 mg	Pharmacist dispenses wrong Auto-injector strength due to lack of clear differentiation on Carton or due to incorrect product selection from shelf.	Outcome: Opioid reversal may be inadequate or re-narcotization may occur more quickly. Additional EVZIO 0.4 mg Auto-Injectors may need to be administered while awaiting emergency medical care. Probability: Depends on the opioid consumed and other factors.	Focused differentiation between Cartons to ensure new color schemes and unique dose color indication for each strength.
	Manufacturer assembles product incorrectly [places wrong Drug Cartridge Assembly in Auto-injector or mislabels Outer Case/Device].	Severity: Depends on the opioid consumed and other factors including whether or not additional EVZIO 0.4 mg are available and how long it takes emergency medical care to arrive.	(b) (4)
	Manufacturer packages wrong naloxone Auto-injector strength in Carton.		
	EVZIO 0.4 mg and EVZIO 2.0 mg both present in the household and caregiver/responder/family member chooses incorrect auto-injector during a suspected opioid emergency	Outcome: Initial opioid reversal may be inadequate or re-narcotization may occur more quickly. Additional EVZIO 0.4 mg or EVZIO 2.0 mg Auto-Injectors may need to be administered while awaiting emergency medical care. Probability: Depends on the opioid consumed and other factors. Severity: Depends on the opioid consumed and other factors, however because multiple EVZIOs are present and can be administered while awaiting emergency medical care, the severity is considered low.	Since multiple EVZIOs will be present in the household to address the possible outcome, no additional (beyond that described above) mitigation is planned.

Risk	Potential Cause	Possible Outcome, Probability & Severity	Planned Mitigation
Patient receives EVZIO 2.0 mg instead of EVZIO 0.4 mg	Pharmacist dispenses wrong naloxone Auto-injector strength due to lack of clear differentiation on Carton or due to incorrect product selection from shelf.	Outcome: A higher dose of naloxone could result in a higher likelihood of adverse events, including withdrawal in patients physically dependent on opioids. Probability: The original Reference Listed Drug (naloxone HCL for injection) was approved with a dosing range of up to 2.0mg initially. Therefore, it is unclear what the likelihood of experiencing adverse events are with a 2.0mg doses versus 0.4mg dose. For the neonate population, the probability is low as it is unlikely a neonate would receive EVZIO given most neonates receive naloxone in a hospital setting. Severity: Since the patient would still receive a clinically meaningful dose of naloxone while waiting emergency medical care, and this dose is within the initial dosing range of other naloxone products, the severity is considered low for most patients. Even if the patient receives both doses of each product (4.8 mg equivalent), the dosing falls within naloxone labeling. ⁵ For neonates, the severity of withdrawal could be high however, the probability of a neonate receiving an injection with EVZIO is low because neonates will be treated in the hospital setting and will likely receive generic naloxone instead.	Focused differentiation between Cartons to ensure new color schemes and unique dose color indication.
	Manufacturer assembles product incorrectly (places wrong Drug Cartridge Assembly in Auto-injector or mislabels Case/Device).	(b) (4)	
	Manufacturer packages wrong Auto-injector(s) in Carton.		

Risk Analysis for EVZIO 0.4 mg and 2.0 mg Product Selection Errors (continued)

Risk	Potential Cause	Possible Outcome, Probability & Severity	Planned Mitigation
Patient receives EVZIO 2.0 mg and EVZIO 0.4 mg	EVZIO 0.4 mg and EVZIO 2.0 mg both present in the household and caregiver/responder/family member chooses incorrect auto-injector during a suspected opioid emergency	Outcome: Same as above scenarios depending on doses required and used. Probability: The likelihood of a household receiving both versions of EVZIO is low. If a patient receives one or more of the EVZIO products, the probability depends on the opioid consumed and other factors. Severity: Since the patient would still receive clinically meaningful dose(s) of naloxone while waiting for emergency medical care, the severity is considered low. Even if the patient receives both doses of each product (4.8 mg equivalent), the dosing falls within naloxone labeling. ⁵ For neonates, the severity of withdrawal could be high; however, the probability of a neonate receiving an injection with EVZIO is low because neonates will be treated in the hospital setting and will likely receive generic naloxone instead.	Carton differentiation and Auto-injector and Outer Case label differentiation in order to guide user to select correct dosage strength.

Results

All 33 participants differentiated the Evzio cartons correctly. Of the 6 laypeople participants that were asked to differentiate the Evzio auto-injectors, 5 participants completed the task correctly. One lay person committed one use error by selecting both the 0.4 mg and 2 mg Evzio autoinjectors when instructed to select the device she was introduced to earlier during the session (i.e. the 2 mg auto-injector).

Participants were asked post-task to identify the characteristics of the Evzio carton that helped them the most to identify the product correctly. Half of the laypeople participants (n=3) identified the specified product primarily by the dose. The other half selected the carton primarily based on color. Two participants reported relying on both color and dosage to select the specified product. Twenty six out of 27 pharmacist and pharmacy technicians identified the primarily the specified product by the dose strength printed near the top of the carton's

principal display panel (PDP). One pharmacist identified the carton primarily by its blue color scheme. Six pharmacists and five pharmacy technicians also mentioned identifying the carton the color scheme. When identifying the auto-injector, four out of six laypeople primarily relied on the color scheme to differentiate the two strengths specifically by matching the auto-injector's color scheme to the carton's color scheme. Two participants checked the dosage on the auto-injector's label to differentiate the two strengths

Root cause analysis

According to the participant, she reported focusing mostly on the auto-injector's blue color during the exploration period and she inaccurately recalled seeing a yellow auto-injector during the exploration period. She selected both auto-injectors (0.2 mg and 4 mg) because she expected the carton to include an auto-injector of each color (i.e. dose strength). In the previous task she did select the correct carton (i.e. 2 mg Evzio carton).

According to (b) (4) they attributed the participant's error to both the auto-injector quantity in the carton and the yellow text for the Evzio brand name on both auto-injectors.

Applicant Conclusions

According to Kaleo, because the participant did not select just one auto-injector and that, during a real opioid overdose emergency, she would be selecting a carton containing two Evzio auto-injectors of the same dose, there is very low risk of a product selection error. In addition, the same participant selected the correct carton dose during the carton selection task. It was determined the residual risk was acceptable and the carton and auto-injector label designs for both Evzio 2 mg and Evzio 0.4 mg have acceptable differentiation.

DMEPA Assessment

- As a result of the root cause analysis, Kaleo, Inc. did not make any changes to the carton labeling or container label for either Evzio 2 mg or 0.4 mg.
- The highest risk for product selection errors is likely to be at the dispensing level (i.e. pharmacists and pharmacy technicians) and no errors were seen in either group.
- The 2 mg strength is being proposed to be indicated as an initial dose for all patient populations, with identical indication and dosage instructions as the currently approved 0.4 mg product. If either were to be accidentally selected over the other, the outcome is of low risk (i.e. overdose or underdose).

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On July 5, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Nursing Community
Search Strategy and Terms	Match Exact Word or Phrase: Evzio

D.2 Results

No cases were identified.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on July 6, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.⁹

Table 3: FAERS Search Strategy	
Date Range	April 3, 2014 to July 6, 2016
Product	Evzio [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search identified 3 cases, of which 3 described errors relevant for this review.

- Other (n=3)
We identified three medication error cases involving accidental exposure to the product. Each case involved patients who accidentally used the device containing actual drug rather than the trainer device. One case involved a 17 year old child who accidentally removed the device with drug versus the trainer from a box during a demonstration on how to treat opioid overdoses by the reporter. No root cause could be determined and no adverse events were reported. The trainer device is marked trainer on top of the

⁹ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

device in uppercase lettering, and it is separated from the devices containing drug within the packaging by the IFU and FPI. The container label is a contrasting color, black and white, compared to the device with drug, (b) (4) white, and purple. The container on the trainer also states, “TRAINER for Evzio” on the principal display panel (PDP). Given the limited number of cases since the drug has been marketed and no reports of adverse events related to the errors, we do not have any risk mitigation strategies to recommend at this time.

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case number	Case version	Manufacturer Control Number	Narrative
11027017	1	US-KALEO, INC- EVZI20150001	<p>INITIAL INFORMATION RECEIVED ON: 27-MAR-2015</p> <p>This is a spontaneous report, received from a consumer, concerning an adult woman of unknown age who accidentally administered EVZIO (naloxone hydrochloride injection) Auto-injector and experienced no adverse reaction.</p> <p>The patient's past medical history, including concomitant medications and allergies, is unknown except for the use of a morphine pump for an unknown chronic pain condition.</p> <p>At about 12:30 AM on 27-MAR-2015 she reported that five minutes previously she had unintentionally applied Evzio with 0.4 mg naloxone auto-injector according to the product instructions, instead of using the trainer auto-injector (without naloxone) when trying to demonstrate to a family member how to use Evzio. She did not notice any adverse reactions. Nine hours later a followup call was initiated and there were still no adverse reactions to report. Specifically, there were no withdrawal syndrome symptoms described.</p>

11890055	1	US-KALEO, INC- EVZI20150014	<p>INITIAL INFORMATION RECEIVED ON: 20-NOV-2015</p> <p>This is a spontaneous report, concerning a 17-year-old male who injected himself with Evzio (naloxone hydrochloride injection) Auto-Injector.</p> <p>On 19-NOV-2015, the reporter was doing a demonstration on the treatment of opioid overdoses with Evzio. He had both the Evzio Auto-injector (naloxone hydrochloride) and Evzio trainer (no drug) with him. A group of students approached him and one student reached into his box, took one Evzio Auto-injector and injected himself in the thigh. It was unknown if the male student knew he was taking the auto-injector with Evzio or the trainer. The student experienced no adverse events at that time. He left the event with friends. The reporter did not know who the student was but did report the incident to the school superintendent who had no additional information about the incident.</p>
12538223	1	US-KALEO, INC- EVZI20160006	<p>INITIAL INFORMATION RECEIVED ON 03-MAY-2016</p> <p>This is a spontaneous report from a medical assistant, forwarded by a sales representative, concerning a 35-year-old woman who accidentally administered one Evzio (0.4 mg naloxone hydrochloride injection) into her thigh, instead of using the trainer. There were no adverse reactions. No additional information was available.</p>

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the

Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX F. SPONSOR'S PREVIOUS QUESTIONS AND DMEPA'S RESPONSES

F.1 Methods

Sponsor's Question 3D (Submitted September 22, 2015):

Does the FDA agree that the proposed Cartons, Outer Case labels, and Device labels provided in this letter sufficiently differentiate the EVZIO 0.4 mg and EVZIO 2.0 mg products?

DMEPA's Response to Question (Dated October 19, 2015):

The acceptability of your proposed carton labeling, outer case labels, and device labels will be a review issue during your NDA submission; however, your approach appears reasonable. Please submit your proposed container labels and carton labeling at the time of your NDA submission.

Sponsor's Question 3D (Submitted September 22, 2015):

Does the FDA agree that the revised Risk Analysis (Table 1) provided in this letter sufficiently addresses the FDA's requests sent to kaleo, Inc. in the FDA's August 7, 2015 letter?

DMEPA's Response (Dated October 19, 2015):

The acceptability of your revised risk analysis will be a review issue during your NDA submission; however, your approach appears reasonable. Please submit your risk analysis at the time of your NDA submission.

Sponsor's Question 3A (Submitted June 29, 2015):

Does the FDA agree that the proposed EVZIO 0.4 mg and EVZIO 2.0 mg Cartons are adequately differentiated to minimize the risk of product selection errors?

DMEPA's Response (Dated July 28, 2015):

The acceptability of your carton labeling will be a review issue during your NDA submission. We recommend you consider in your risk analysis the possibility that healthcare providers and patients who are already familiar with the currently marketed Evzio 0.4 mg strength may recall the dominant purple color present on the carton labeling and container labels. Based on negative transfer, healthcare providers and patients may select the purple carton labeling thinking that it is Evzio 0.4 mg, when it is the proposed Evzio 2 mg strength.

Sponsor's Question 3B (Submitted June 29, 2015):

Does the FDA agree that the proposed EVZIO 0.4 mg and EVZIO 2.0 mg Device and Outer Case labels are adequately differentiated to minimize the risk of product selection errors?

DMEPA's Response (Dated July 28, 2015):

The acceptability of your container labels will be a review issue during your NDA submission. However, using a similar purple (b) (4) color scheme for both the Evzio 0.4 mg strength and proposed 2 mg strength on the container labels is vulnerable to confusion and product selection errors. The risk for product selection errors between the two strengths as currently presented is increased if the devices are stored without their cartons. Please see the response to Question 3A.

Sponsor's Question 3C (Submitted June 29, 2015):

Does the FDA have any concerns regarding the planned additional changes to the EVZIO label components?

DMEPA's Response (Dated July 28, 2015):

See responses above.

Sponsor's Question: (Submitted September 26, 2014):

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?

DMEPA's Response (Dated December 8, 2014):

This is a review issue; however, using a purple (b) (4) color scheme for both the NAI-HP and EVZIO device label and case and carton labeling 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.

F.2 Results

The Sponsor has taken into consideration all of our preliminary concerns regarding product selection errors and negative transfer as a result of the similarity of the color scheme between the two strengths, 0.4 mg and 2 mg. The updated color scheme provides a more clear differentiation between the two strengths (see Appendix G). In addition, they also took into

consideration the possibility of healthcare providers and caregivers/patients selecting the wrong strength into their risk analysis and have addressed the concerns (see Appendix C).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹⁰ along with postmarket medication error data, we reviewed the following Evzio labels and labeling submitted by Kaleo, Inc. on April 19, 2016.

- Container label
- Carton labeling
- Instructions for Use
- Trainer Instructions for Use

G.2 Label and Labeling Images



¹⁰ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

MONICA M CALDERON
09/22/2016

BRENDA V BORDERS-HEMPHILL
09/22/2016

QUYNHNHU T NGUYEN
09/22/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205787/S-007 BLA#	NDA Supplement #: S- 007 BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input checked="" type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: EVZIO Established/Proper Name: naloxone hydrochloride injection Dosage Form: auto injector Strengths: 0.4mg; 2mg (proposed)		
Applicant: kaleo, Inc Agent for Applicant (if applicable):		
Date of Application: April 19, 2016 Date of Receipt: April 19, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: October 19, 2016		Action Goal Date (if different):
Filing Date: June 18, 2016		Date of Filing Meeting: May 18, 2016
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): No change in indication; New strength, 2mg is proposed		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 112292

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Priority goal dates will be triggered by entering the filing letter in DARRTS.
Are the established/proper and applicant names correct in electronic archive? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into electronic archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Priority designation not in DARRTS yet. Priority date will be triggered by filing letter.
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.			X	
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid – Note: Sponsor plans to request a refund. User Fee Staff was consulted and Sponsor was informed that they appear to be eligible and should apply for a refund. <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:	<input checked="" type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>																	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>																	

If yes, # years requested:				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Document was requested from the Sponsor. Sponsor updated NDA.
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Electronic submission
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This is a supplement
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Review being requested in the filing letter.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	DRISK not required for this application.
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Outer carton label <input checked="" type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH ; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH – Devices CDRH- Compliance Pediatrics Maternal Health
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Date of meeting: December 8, 2014 Date of minutes: December 23, 2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-supplement
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 18, 2016

BACKGROUND: The Sponsor is proposing to add a higher strength (2 mg), and has submitted additional clinical pharmacology and pediatric information, besides the CMC information. They have also submitted updated device information and packaging information and will be updating the label to PLLR (required).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diana Walker	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Joshua Lloyd		Y
Division Director/Deputy	Sharon Hertz		Y
	Ellen Fields		Y
Office Director/Deputy	Curt Rosebraugh		N
	Mary Parks		N
Clinical	Reviewer:	Elizabeth Kilgore	Y
	TL:	Joshua Lloyd	Y
Clinical Pharmacology	Reviewer:	Wei Qiu	Y
	TL:	Yun Xu	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carlic Huynh	Y
	TL:	Beth Bolan Dan Mellon	Y Y
Product Quality (CMC) Review Team:	ATL:	Zedong Dong	Y
	RBPM:	Hongly La	N
• Drug Substance	Reviewer:	Pat Maturu	N
• Drug Product	Reviewer:	Pat Maturu	N
• Process	Reviewer:	tbd	
• Microbiology	Reviewer:	tbd	
• Facility	Reviewer:	tbd	
• Biopharmaceutics	Reviewer:	Duan Peng Haritha Mandula	Y Y
• Other (e.g., Branch Chiefs, EA Reviewer)	CDRH devices and compliance to be determined		
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	tbd	
	TL:	tbd	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	tbd	
	TL:	tbd	
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Monica Calderon	Y
	TL:	Vicky Borders-Hemphill	Y
Other attendees	Davis Mathew (OSE RPM)		Y
	Shelly Kapoor (RPM)		Y
	Adebola Ajao (DEPI)		Y
	Jennifer Nadel (Medical Officer)		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none">• 505 b)(2) filing issues:<ul style="list-style-type: none">○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none">• Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none">• Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> No comments</p>

<p>CLINICAL</p> <p>Comments: Annotated labeling</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: Will be part of a multiple NDA AC to discuss the appropriate naloxone dose or use for multiple dose strengths in the community.</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: October 6 or 7, 2016 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: Literature review for PLLR</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Issues sent via email in advance, reminder of commitment to submit by specified date added to the filing letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity</u> (NDAs only)</p> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<ul style="list-style-type: none">• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	<input type="checkbox"/> YES <input type="checkbox"/> NO
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REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Sharon Hertz	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 19, 2016	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Wrap-Up – September 22, 2016	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

DIANA L WALKER
06/08/2016

PARINDA JANI
06/08/2016