CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215457Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 112292

MEETING MINUTES

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

Attention: Shelly Shirkey
Senior Manager, Regulatory Affairs

Dear Ms. Shirkey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Act and your New Drug Application (NDA) 209862 for EVZIO (naloxone HCl injection, USP) Auto-Injector.

We also refer to the meeting between representatives of your firm and the FDA on February 24, 2020. The purpose of the meeting was to seek input from the Agency that the proposed studies and information to be submitted under sNDA will adequately support the development and approval of NAI 10 mg.

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

If you have any questions, call me at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Swati Patwardhan
Regulatory Project Manager
Anesthesiology, Addiction Medicine
and Pain Medicine
Division of Regulatory Operations for Neuroscience
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Feb. 24, 2020, 3:00 to 4:00 p.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, MD 20903

Application Number: IND 112292
Product Name: EVZIO (naloxone HCl injection, USP) Auto-Injector

Indication: (b) (4)

Sponsor Name: kaleo, Inc.

Meeting Chair: Rigoberto Roca, MD, Director (Acting), Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)
Meeting Recorder: Swati Patwardhan, Regulatory Health Project Manager, Division of Regulatory Operations for Neuroscience (DRO-N)

FDA ATTENDEES

- Rigoberto Roca, MD, Director (Acting), DAAP
- Naomi Lowy, MD Deputy Director (Acting), DAAP
- Emily Deng, MD, Clinical Team Leader (Acting), DAAP
- Jennifer Nadel, MD, Medical Officer, DAAP
- Dan Mellon, PhD, Nonclinical Supervisor, Division of Pharmacology/Toxicology for Neuroscience (DPT-N)
- Newton Woo, PhD, Nonclinical Team Leader, DPT-N
- Carlic Huynh, PhD, Nonclinical Reviewer, DPT-N
- Yun Xu, PhD, Team Leader, Division of Clinical Pharmacology II (DCP2), Office of Clinical Pharmacology (OCP)
- Wei Qiu, PhD, Clinical Pharmacology Reviewer, DCP2, OCP
- Zedong Dong, PhD, Team leader, Division of Postmarketing Activities I (DPMAI), Office of Pharmaceutical Quality (OPQ)
- Daneli LopezPerez, PhD, Chemistry Reviewer, DPMAI, OPQ
- Swati Patwardhan, Regulatory Health Project Manager, DRO-N

- Brad Leissa, MD, Deputy Director, Counter-Terrorism and Emergency Coordination Staff (CTECS)
- Gayle Tuckett, PharmD, CTECS
- Matthew Hornung, PharmD, CTECS
- Millie Shah, PharmD, Team Leader, Division of Medication Error and Prevention Analysis (DMEPA)
- Jason Flint, Safety Evaluator, DMEPA
- Rumi Young, PhD, Team Leader, Center for Devices and Radiological Health (CDRH)
- David Wolloscheck, PhD, Devices Reviewer, CDRH

SPONSOR ATTENDEES

- Ronald Gunn, Chief Operating Officer kaleo, Inc.
- Glen Kelley VP, Regulatory Affairs, kaleo, Inc.
- Charles Nicholls, VP, Global Supply Chain and Manufacturing, kaleo, Inc.
- Catherine Kessler, PhD, Associate Director, Clinical Development, kaleo, Inc.
- Michael Roe, Sr. Director, Product Development and Industrialization, kaleo, Inc.
- Michelle Shirkey, Sr. Manager, Regulatory Affairs, kaleo, Inc.
- Jennifer C. Dabisch, PMP, Deputy, Senior Director Medical Regulatory One Network of Excellence for Regulatory Affairs and Quality Assurance (ONE-RAQA) Supporting DTRA JSTO-CB & JPEO-CBRND
- [redacted] (b) (4) Contract Support for Department of Defense
- Saumil Shah, Assistant Product Manager, Chemical Defense Pharmaceuticals
- LTC Kara Schmid, Joint Product Manager, Chemical Defense Pharmaceuticals
- [redacted] (b) (4) Contract Support for Department of Defense

BACKGROUND

Evzio (naloxone HCl injection) Auto-Injector for intramuscular or subcutaneous use, 2 mg, was approved in October 2016 under NDA 209862. On October 31, 2019, the Sponsor requested a Pre-sNDA meeting to seek input from the Agency if the proposed studies and information to be submitted under sNDA will adequately support the development and approval of naloxone autoinjector (NAI) 10 mg. The meeting request was to discuss:

i. If NAI 10 mg could be submitted as a supplement to NDA 209862

ii. If the development program proposed will support the proposed product labeling for NAI 10 mg

iii. The development requirements for NAI 10 mg to support submission of a supplemental NDA (sNDA) adequate for FDA review

The briefing package was submitted along with the meeting request. The Sponsor amended the briefing package on January 17, 2020, to include newly obtained manufacturing performance and analytical results.

FDA sent Preliminary Comments to the Sponsor on February 21, 2020. Prior to the meeting, in the email dated February 24, 2020, the Sponsor requested clarification to the responses related to General comments for the clinical development program, questions 10, 14, 21, and 24.

DISCUSSION

The questions from the briefing package is reproduced below in Arial *italics,* the FDA responses are in Arial **bold** font, the Sponsor's pre-meeting comments are in Times New Roman regular font, where is the meeting discussion is in regular Arial font.

Regulatory and Administrative Background Information

General comments for the clinical development program:

1. **Your proposed indication is different from that proposed by the Department of Defense (DoD) under PIND 141770. Under PIND 141770, this product was intended to be developed** (b) (4)

   You have not provided data (b) (4)

2. **Because the 10-mg naloxone autoinjector is a Public Law 115-92 priority drug for the Department of Defense, FDA would like to confirm that kaleo's proposed indication and device presentation meets DoD's operational needs for the warfighter.**

3. **You have stated that you plan to use a similar regulatory approach to development as you used for Evzio 2 mg (NDA 209862). With that development, you discontinued marketing Evzio 0.4 mg (NDA 205787) after approval of Evzio 2 mg. Clarify if you intend to continue marketing the 2 mg product if the 10-mg product is approved. If you intend to market both**

products, consider how you plan to differentiate them with labeling, such as indications, dosage, and administration.

4. (b) (4) **However, your proposed 10 mg product** (b) (4) **Elimination of these features may be appropriate for military use** (b) (4)

Sponsor's Pre-meeting Response
Based on FDA's feedback and discussion with the DoD, kaleo, Inc. seeks to expedite approval of NAI 10 mg for the indication originally proposed by the DoD (b) (4) as the highest priority. This would include use by those at risk for exposure to ultra-potent opioids such as the military and law enforcement agencies such as the Drug Enforcement Agency. (b) (4)

Meeting Discussion:
The Sponsor acknowledged that the DoD indication was for warfighters, and the change in the indication (b) (4) They agreed to adopting the DoD proposed indication (under PIND 141770). (b) (4) (b) (4)

Question 1:
Does the FDA agree that NAI 10 mg should be submitted as a supplement to NDA 209862?

FDA Response to Question 1:
No, we do not agree. As you plan to have different labeling, changes to your device (b) (4) **new instructions for using the device, and new human factors studies, the application for this product should be submitted under a new NDA.**

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 2:
Does the FDA agree that the sNDA for NAI 10 mg as proposed herein would not contain Clinical Data and therefore would only be assessed a one-half PDUFA fee for its review?

FDA Response to Question 2:
Please refer our response to Question 1. A new NDA will require a PDUFA fee. For the financial year 2020 fee schedule, refer to the following: https://www.federalregister.gov/documents/2019/08/02/2019-16435/prescription-drug-user-fee-rates-for-fiscal-year-2020.
If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, and contain new clinical data, the application will be subjected to full fee. A final determination will be made upon receipt of your application.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 3:
Does the FDA agree that NAI 10 mg is considered a medical countermeasure and should expedite the development and review (i.e., rolling review; priority review) under P.L. 115-92?

FDA Response to Question 3:
FDA understands that the NAI is a DoD priority drug under P.L. 115-92 and therefore is eligible to be reviewed in a manner similar to products under the breakthrough therapy designation (BTD). Products that receive BTD are eligible for:

- **Fast Tract designation features**
- **Intensive guidance on an efficient drug development program, beginning as early as Phase 1**
- **Organizational commitment involving senior managers**
- **Rolling review**

A request for a Priority Review designation will need to be evaluated with your NDA submission. The qualifying criteria for this designation include:

- **An application for a drug that treats a serious condition AND, if approved, would provide a significant improvement in the safety or effectiveness OR**

- **Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR**
- **An application for a drug that has been designated as a qualified infectious disease product OR**
- **Any application or supplement for a drug submitted with a priority review voucher**

Your request should include rationale for why your product meets these criteria, specifically why your product would provide a significant improvement in safety or effectiveness over approved products.

To obtain preliminary Agency agreement on your proposal for Fast-track/Rolling Review, submit a request according to the guidance for industry*: Expedited Programs for Serious Conditions – Drugs and Biologics*, available at https://www.fda.gov/media/86377/download.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 4:
Does the FDA agree with the approach outlined in Figure 1 regarding compliance with PREA for NAI 10 mg?

FDA Response to Question 4:
No, we do not agree with your proposed plan. (b) (4) **Although conducting pediatric studies may not be feasible for the reasons you stated, your application must still contain a pediatric assessment, which may be based on other available data (e.g., published literature, leveraging existing pediatric information from the approved labeling for the reference product). Your required pediatric assessment must address the following issues:**

- **The safety and effectiveness of the proposed dose of naloxone for all pediatric age ranges, including neonates**
- **A device that can appropriately deliver the correct dose to all pediatric patients, including neonates**

Your PSP should state that you plan to submit a pediatric assessment with your NDA that addresses the above issues. Your PSP should also state that you will

submit proposed pediatric labeling for the proposed product based on this pediatric assessment with your planned NDA and that you plan to label your product down to birth. If you cannot provide data to support this product in all pediatric age groups, it may impact the approvability for your product.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 5:
Does the FDA agree with the proposed Table of Contents (Appendix 1) for the NAI 10 mg sNDA?

FDA Response to Question 5:

Please refer to our response to Question 1 regarding the most appropriate regulatory pathway. Questions regarding a Table of Contents are premature, as you have not submitted any data.

Your NDA submission should submit PK datasets including raw PK and PK parameters and bioanalytical reports.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Labeling

Question 6:
Does the FDA agree with the proposed changes in the dosage and administration instructions of the Prescribing Information (Section 2.1) for NAI 10 mg (b) (4) (b) (4) *?*

FDA Response to Question 6:
We are unable to answer this question due to the limited information provided in the meeting package. The final determination of the proposed changes will occur after we review the data from the human factors validation study.

In your NDA submission, describe realistic circumstances that may occur (b) (4)

Further comments on appropriate labeling will be provided after your NDA submission.

Meeting Discussion:

The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 7:
Does the FDA agree [redacted] *for NAI 10 mg?*

FDA Response to Question 7:
As mentioned in our responses to Question 1 and 3, you have not provided data to justify the need for NAI 10 mg [redacted] **This section in labeling will be reviewed after your NDA submission. Your NDA submission should clearly describe the pharmacodynamic and pharmacokinetic data that support your statement in this section.**

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 8:
Does the FDA agree [redacted] *described in Section 1.13.6.3 into the* [redacted] *section* [redacted] *of the proposed Prescribing Information?*

FDA Response to Question 8:
No, we do not agree. [redacted]

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Chemistry, Manufacturing and Controls

Question 9:
Does FDA agree that the proposed specifications and acceptance criteria for NAI 10 mg are appropriate for initiation of the clinical study and sNDA review?

FDA Response to Question 9:
The proposed specifications and acceptance criteria appear to be reasonable. The final determination of acceptability will be determined after review of the data.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 10:
Does the FDA agree that the registration stability program can be conducted (b) (4) *?*

FDA Response to Question 10:
We recommend that you use three registration batches of the final finished product (including the device constituent parts) for the registration stability program. In addition, we recommend that you provide twelve months and six months of stability data, respectively, for long-term and accelerated storage conditions in the initial submission. The Agency recommends that you reference ICH Q1E for shelf life determination. Provide statistical analysis to support the proposed expiry as necessary. It appears to be reasonable to use one lot of the finished product for temperature cycling and photostability studies.

Sponsor's Pre-meeting Response
Based on the extensive historical results with NAI 0.4 mg and NAI 2 mg showing no difference in the drug stability between the Drug Constituent (i.e., filled drug cartridges) and the final finished product (including device constituent parts), kaleo, Inc. proposes an alternative to FDA's recommendation that includes an additional Device Constituent Accelerated Aging study

NAI 0.4 mg and NAI 2 mg Long-Term Stability Overview
The following long-term (LT) stability data is available for NAI 0.4 mg and NAI 2 mg:

- Drug Constituent (i.e., filled drug cartridges)
  - Two batches of 1 mg/mL naloxone HCl Drug Constituent – up to 48 months LT stability data
  - Five batches of 5 mg/mL naloxone HCl Drug Constituent – up to 48 months LT stability data
- Finished Product (including Device Constituent)
  - Three NAI 0.4 mg finished product development batches – 48 months LT stability data
  - Five NAI 0.4 mg finished product commercial batches – up to 36 months LT stability data
  - One NAI 2 mg finished product development batch – 36 months LT stability data

- Five NAI 2 mg finished product commercial batches – up to 24 months LT stability data

In all studies to date, the drug stability profile of the Drug Constituent is the same as the finished product; therefore, 12-month LT results in three final finished product lots should not be required to support review and approval of the initial submission.

To provide additional assurance that the Device Constituent is not impacted by the new 25 mg/mL naloxone HCl Drug Constituent, kaleo, Inc. proposes to conduct an Accelerated Aging study (b) (4) as part of the *in vitro* verification program. This study will include (b) (4)

Kaleo, Inc. Clarifying Question 10

Does the FDA agree that the revised stability program summarized below will be sufficient for the initial submission, and if the data supports, approval of NAI 10 mg?

- One Technical batch of Drug Constituent LT (12 months) and accelerated (Acc.) (6 months) stability (to support drug stability)
- Two Registration batches of Drug Constituent LT (12 months) and Acc. (6 months) stability (to support drug stability)
- One Registration batch of finished product LT (6 months) and Acc. (6 months) stability (to support drug and device stability)
- One Registration batch of Device Constituent Accelerated Aging (60°C) study (equivalent to 36 months) (to support device stability)
- One Registration batch of finished product Temperature Cycling study

Meeting Discussion:
Referring to their pre-meeting response, the Sponsor reiterated that the available long-term stability data for the 0.4 and 2 mg NAI can help bridge the stability for 10 mg NAI. Additionally, they plan to do an accelerated aging study for the device shelf life to ensure that it does not affect the in vitro performance. The Division noted that because of the higher concentration, differences in the viscosity of the drug constituent may impact device performance. The Sponsor responded that due to a wide safety margin for the device, they do not anticipate that the higher concentration for NAI 10 mg will affect the performance. The Division agreed with the proposed approach.

Question 11:

Does the FDA agree that the sNDA can be reviewed based on 12 months of 25 mg/mL Drug Constituent stability data and 6 months stability data of NAI 10 mg?

FDA Response to Question 11:
See our preliminary response to Question 10.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 12:
If no differences in stability trends compared to EVZIO are observed, does the FDA agree the proposed shelf life for NAI 10 mg will be 24 months (b) (4) *consistent with ICH Q1E?*

FDA Response to Question 12:
See our preliminary response to Question 10.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 13:
Does the FDA agree that the 40°C/75% RH stability studies in combination with the temperature cycling studies are sufficient to support labeling regarding temperature excursions?

FDA Response to Question 13:
The approach appears to be reasonable. The adequacy of the studies to support the proposed labeling will be determined after review of the data.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 14:
Does the FDA agree that a new leachables analysis of one batch of the NAI 10 mg Drug Constituent Component along with the previous extractables and leachable studies of EVZIO are sufficient to meet the FDA/USP requirement for leachables evaluation?

FDA Response to Question 14:

Your extractables evaluation should include extraction media with higher and lower pH bracketing pH (b) (4) In addition, volatile extractables should be evaluated as part of the extractables study and should be monitored in the finished drug product if necessary.

Provide justification that the higher concentration of naloxone in this product does not alter the leachable profile. Ensure that your extraction study analytical methods are able to identify and quantitate compounds present at 5 mcg/day or higher based on a presumed maximum daily dose of 20 mg (two injections). To obviate the need for new leachable assessments over the course of stability provide bridging data to support your conclusion that the leachable profile for this higher concentration formulation is not altered when compared to the currently approved product.

Sponsor's Pre-meeting Response:
The pH specification for the Drug Constituent component is (b) (4) while the pH specification for the finished product is 3.0 – 4.5 for both release and stability testing. Previously conducted extractables testing on the (b) (4) gray plungers and seals was conducted using the nominal pH (b) (4) of the Drug Constituent component.
Based on the FDA's preliminary advice, kaleo, Inc. proposes the following changes to the study plan for Extractables and Leachable testing:

- Conduct extractables testing in extraction media using pH 3.0 and 4.5 that will cover the full range of the finished product specification
- Evaluate and compare the results of these studies to the previous extractables study of the container-closure components and the two stability leachable studies (one for NAI 0.4 mg and one for NAI 2 mg)
- Determine if the results provide adequate bridging data or if a new stability leachable study for NAI 10 mg is necessary

Kaleo, Inc. Clarifying Question 14
Does the FDA agree that the revised Extractables and Leachables testing plan is consistent with and meets the FDA's advice?

Meeting Discussion:
The Division asked if the Sponsor have any leachable data with the 10 mg NAI product. The Sponsor noted that they do not have leachable data with 10 mg NAI. The Division commented that comparing extraction studies between the lower and higher concentration products may be useful and can help to inform the leachable profile but strongly recommended that the Sponsor obtain and submit leachable data to support the safety of the higher concentration configuration. However, the adequacy of the submitted extractable/leachable data to support approval of an application can only be determined upon review of the complete submission of the NDA. review. If these data are not adequate, further extractable/leachable assessment may be required, possibly as a post-marketing requirement depending on the review of the data. The Division also

suggested comparing the 10 mg NAI accelerated stability results with the approved product.

Question 15:
Does the FDA agree that the elemental impurity risk assessment meets all the FDA requirements and no additional assessments are needed?

FDA Response to Question 15:
Provide the detailed elemental impurity risk assessment report in the submission. This will be a review issue.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Device Constituent

Question 16:
Does the FDA agree that the testing plan in Table 10 is adequate and that no additional in vitro verification testing is required to support the review and approval of NAI 10 mg?

FDA Response to Question 16:
You stated that the new device presentation does not include the electronic assembly (b) (4) **The proposed bench testing appears reasonable given that you provide a comparison of the 2 mg and 10 mg device and a rationale of how any changes do not impact the performance attributes you are proposing to leverage.**

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 17:
Does the FDA agree that NAI 10 mg can rely on the Device Reliability data for EVZIO 2 mg?

FDA Response to Question 17:
You are proposing (b) (4)

(b) (4)

While we agree that leveraging some or all of the reliability data of the 2 mg presentation may be possible, you should address all potential performance differences between the two presentations and your proposed testing of the 10 mg presentation should be supportive of the overall reliability specification. Additionally, for any differences in the manufacturing (e.g., different manufacturing line or materials), you should provide supporting information that this change does not affect the overall reliability of the device. Note that if you identify differences in the performance of the two presentations, additional information may be necessary to demonstrate device reliability.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Human Factors Engineering

Question 18:
Does the FDA agree that the Human Factors Engineering approach for NAI 10 mg (b) (4) *is appropriate to support the review and approval of the NAI 10 mg sNDA?*

FDA Response to Question 18:
We agree that you will need to validate your proposed product by conducting a human factors (HF) validation study, however, the appropriateness of the HF approach will be a review issue because we have not reviewed your use-related risk analysis, HF validation study protocol, or HF validation study results.

We note that you use the terms (b) (4) (b) (4) **however, these terms are not defined, so it is not clear how these proposed studies might differ from an HF validation study.**

We recommend that you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. For example, you may consider the risk of negative transfer of learning between Evzio with the EPS, and your proposed product without the EPS.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating

the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

The risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible.
Refer to our draft guidance titled *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*[1] for the content of a human factors validation study protocol submission.

Submit the requested information as an amendment to the IND, in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures can be found in the following guidance documents[2]:

> ***Applying Human Factors and Usability Engineering to Medical Devices***
>
> ***Guidance on Safety Considerations for Product Design to Minimize Medication Errors***

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling[2]:

> ***Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development***
>
> ***Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors***
>
> ***Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications***

Meeting Discussion:

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 19:
Does the FDA agree that the Human Factors Engineering approach is appropriate to validate the NAI 10 mg package configuration of a carton containing a single NAI with FDA-approved labeling?

FDA Response to Question 19:
With regard to the HF Engineering approach, please see our response to Question 18 above. Additionally, it is premature to agree with your human factors engineering approach because it is unclear whether you are proposing the NAI 10 mg package configuration containing a single NAI (b) (4) (b) (4) (b) (4) **Given that NAI 10 mg provides a high dose and the possibility of underdosing may be low, a single-dose unit package for NAI 10 mg may be appropriate provided that the proposed HF study demonstrates that the incidence of administration error is low enough to meet the current regulatory standard.**

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 20:
Does the FDA agree that no additional Human Factors Engineering studies are required to support approval of a bulk package configuration for NAI 10 mg?

FDA Response to Question 20:
We note that the number of autoinjectors in the bulk package configuration is "to be determined". We are unable to comment on whether additional HF validation studies might be needed to support approval because we do not know whether the configuration of the bulk packaging introduces new use tasks or use-related risks compared to the individual packaging. When you have determined the bulk packaging configuration, you should conduct a comprehensive use-related risk analysis. Based on this risk analysis, you will need to determine whether you need to submit the results of a human factors (HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Nonclinical (Toxicology)

Question 21:
Does the FDA agree that no additional nonclinical toxicology studies are necessary to initiate the clinical study or for sNDA review for NAI 10 mg?

FDA Response to Question 21:
No, we cannot agree at this time. Your meeting package does not address how you will justify the local and systemic safety of the higher concentration and higher dose associated with your product as compared to the referenced product. It may be possible to leverage prior clinical experience or literature that tested higher concentration/dose to justify the safety in lieu of new nonclinical toxicity studies. However, if an adequate scientific justification cannot be provided, nonclinical toxicology studies per ICH M3(R2) are required. In the case of your product that exceeds the concentration of other approved naloxone products, a repeat-dose toxicity study in a single species will be required to support local safety. For a product that results in systemic exposures (C_{max} or AUC) that exceeds the highest labeled use of a referenced naloxone product, repeat-dose toxicity studies in two species (one rodent and one nonrodent) will be required to support systemic safety. We note that recent publications have highlighted that pulmonary complications in opioid overdose subjects who were treated with naloxone occur and are more likely to occur in patients receiving a higher total dose of naloxone. Therefore, when you address the systemic safety of your product, discuss how this clinical signal is not a concern with your product. This may entail conducting a nonclinical study that evaluates the interaction of opioids and naloxone.

Sponsor's Pre-meeting Response
The FDA-approved labeling for naloxone HCl injection for use in adults for treatment of known or suspect opioid overdose recommends an initial dose of 0.4 mg to 2 mg naloxone HCl administered intravenously, if possible. If the desired degree of improvement in respiratory function is not obtained, dosing can be repeated at 2 to 3-minute intervals, and if no response is observed after 10 mg of naloxone HCl has been administered, the diagnosis of opioid-induced respiratory depression should be questioned. The FDA-approved labeling for the reference product does not place a limit on the total amount of naloxone HCl that can be administered. In studies of ischemic stroke and septic shock, naloxone HCl has been administered to patients in doses much greater than 10 mg with no untoward side effects and with resulting plasma naloxone concentrations that far exceed the anticipated systemic exposure for NAI 10 mg.
The reference product, naloxone HCl injection (NDA 016636) completed the repeated-dose toxicity studies summarized in Table 1. The human equivalent dose for these studies

significantly exceeds the proposed NAI 10 mg dose. Furthermore, studies conducted in rat and monkey were administered via subcutaneous administration. No local safety signals were noted other than injection site irritation at the 200 mg/kg dose group of rats treated for 4 weeks.

Naloxone auto-injector 10 mg utilizes the same excipient, injection volume, and Device Constituent as NAI 0.4 mg and 2 mg, only differing in the naloxone concentration. Therefore, kaleo, Inc. anticipates NAI 10 mg will have a similar innocuous local tolerability profile. Furthermore, the lack of injection site reactions observed in the nonclinical toxicology studies, where substantially higher naloxone HCl doses were used, supports that nonclinical local tolerance studies should not be required for initiation of the clinical study.

Table 1 Repeated Dose Toxicity Studies of Naloxone HCl

Species (Number and Sex)	Duration (Route)	Dose Level (mg/kg)	Human Equivalent Dose (mg/kg)	Human Dose (mg/60 kg)	Significant Observations
Rat (6M)	3 weeks (SC)	100	16.1	966	Transient salivation and partial ptosis. No findings at autopsy. Slight weight decrease
Rat (10M, 10F)	4 weeks (SC)	10	1.6	96	No significant observations
		50	8.1	486	Salivation
		200	32.3	1938	Slight body weight decrease in males. Excess salivation, tremors, and tonic-clonic convulsions. Injection site irritation
Monkey (2M, 2F)	30 days (SC)	5	1.6	96	No significant observations
		20	6.5	390	Lethargy, slight tremors, ataxia
		60	19.4	1164	Tremors, vocalization, postural depression, some emesis, some analgesia, tonic-clonic convulsions
Dog (2M, 2F)	14 day (IV)	0.2	0.1	6	No significant observations
		0.6	0.3	18	Transient hind limb weakness
		4	2.2	132	Transient hind limb weakness

Source: NDA 016636 (*Summary Basis of Approval – NARCAN*, FDA, 1971)
Abbreviations: F = female; IV = intravenous; M = male; SC = subcutaneous

Kaleo, Inc, Clarifying Question 21a:
Does FDA agree that the nonclinical toxicology studies referenced through NDA 016636 that include doses far exceeding the proposed NAI 10 mg dose, are adequate to justify initiation of the clinical study?

Kaleo, Inc. Clarifying Question 21b:
Does the FDA agree that no additional nonclinical toxicology studies are required to support the local and systemic toxicity profile of the 25 mg/mL naloxone HCl drug solution for NAI 10 mg?

Meeting Discussion:
The Division responded that because the Sponsor does not own the underlying nonclinical data for the referenced Narcan product, they can only rely on the Agency's

previous findings of safety and efficacy related to Narcan product approved under NDA 016636, as reflected in the label. The Division also commented that data found in the summary basis of approval cannot be relied upon for an NDA submission. However, the Division informed the Sponsor that information in the summary basis of approval may be leveraged to support clinical studies during the IND stage. Further, if the Sponsor wants to submit local and systemic safety data based on the clinical study, the Sponsor will have to appropriately justify why it is adequate to support the proposed higher doses. The adequacy of the data can only be determined upon review of the complete submission.

Nonclinical (Pharmacology and *In vivo* Studies)

Question 22:
Does the FDA agree that no additional nonclinical in vivo pharmacology studies are required to support the review and approval of the NAI 10 mg sNDA?

FDA Response to Question 22:
We agree that no new in vivo pharmacology studies will likely be required for approval of an NDA submission. However, additional nonclinical studies may be required to support the review and approval of your proposed naloxone autoinjector (see our response to Question 1).

We acknowledge that the DoD has conducted several nonclinical studies to understand the physiology and behavioral responses of non-human primates when administered naloxone after carfentanil exposure. Submit final study reports for these studies that describe the methodologies used, endpoints evaluated, and include all raw data collected.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Clinical

Question 23:
Does the FDA agree with kaleo, Inc.'s approach that successful completion of a bioavailability, dose-proportionality study of NAI 10 mg and EVZIO 2 mg will be sufficient to provide the necessary pharmacokinetic data to support review and approval of the NAI 10 mg sNDA?

FDA Response to Question 23:
In general, your approach appears appropriate. However, if your product demonstrates a substantially higher systemic exposure than the reference

product (and this is expected in your proposed study), additional data or justification may be required to assure that the higher exposure does not represent a safety concern (e.g., from literature or pharmacokinetic data for the reference naloxone product administered at the higher approved doses), especially for opioid-dependent patient population and the pediatric population.

It appears reasonable to conduct a dose proportionality study to characterize the PK of your proposed NAI 10 mg and assess the dose proportionality with your approved EVZIO 2 mg. You stated that partial AUCs will be calculated to compare the early absorption phase but did not mention the PK sampling time points. Collect the first blood sample around 2.5 min post-dose to characterize the early absorption phase. Since onset of action is critical for reversal of opioid overdose, it is expected that at early absorption phase, the naloxone exposure for the 10 mg product will be comparable or higher compared to the 2 mg product, from the first blood sampling time point (e.g., 2.5 min).

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Question 24:
Does the FDA agree that monitoring of standard safety parameters in the proposed bioavailability, dose-proportionality study will be sufficient to support review and approval of the NAI 10 mg sNDA?

FDA Response to Question 24:
See responses to Questions 3 and 23 regarding concerns of your product providing exposures significantly exceeding the reference product. Additionally, it is premature to comment on the sufficiency of safety monitoring for a future protocol, as you have not provided the clinical protocol for your proposed study. In general, for naloxone studies we recommend:

a. **Enrollment of otherwise healthy male and female volunteers who are not opioid dependent**
b. **ECGs**
c. **Cardiac monitoring**
d. **Monitoring of vital signs**
e. **Local injection site reaction monitoring**

When you submit your protocol for your IND, we will evaluate it for safety and provide further feedback at that point.

Sponsor's Pre-Meeting Response:

We acknowledge the FDA's response and plan to submit the pharmacokinetic, bioavailability study protocol for FDA review and comment prior to submitting the final protocol to the IND.

Meeting Discussion:
The Division asked the Sponsor to submit the draft protocol with adequate toxicological justification to the current existing IND. The Division expressed concerns that there will be no 30-day review clock for draft protocol review and reminded the Sponsor that an advice letter will be sent before they finalize the clinical protocol. The Sponsor agreed that the study will be initiated after they have received the advice letter and the protocol is finalized. The Division also reminded the Sponsor to submit the human factors study protocol under the IND for Division's review.

Question 25:
Does the FDA agree that clinical evaluation of local tolerability at the injection site in the proposed bioavailability, dose-proportionality study is adequate to support review and approval of the NAI 10 mg sNDA?

FDA Response to Question 25:
No, we do not agree. Please see our response to Question 21.

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

ADDITIONAL COMMENTS:

Nonclinical

We have the following additional comments to assist in your preparation of an IND and NDA submission:

IND submission:

1. **We remind you that new excipients must be adequately qualified for safety. As noted in the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at https://www.fda.gov/media/72260/download, "the phrase new excipients means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety**

data with respect to the currently proposed *level of exposure, duration of exposure, or route of administration*." (emphasis added).

- **Published literature to support the safety of an excipient rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.**

- **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your excipient. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel excipient.**

2. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at: https://www.fda.gov/media/85885/download. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.**

NDA submission:

3. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds must be adequately justified for safety from a toxicological perspective.**

4. **Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for local and systemic safety as per ICH Q3A(R2) or ICH Q3B(R2). In order to provide adequate qualification:**

    a. **You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

    b. **In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14-days should be completed.**

        Refer to

        Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*
        https://www.fda.gov/media/71727/download

        and

        Guidance for industry: *Q3B(R2) Impurities in New Drug Products*
        https://www.fda.gov/media/71733/download

5. **Your NDA must adequately address the safety of residual solvents in accordance with the ICH guidance document, *Q3C(R6): Residual Solvents*, available at https://www.fda.gov/media/71736/download.**

6. **Your NDA must adequately address the safety of elemental impurities in accordance with the ICH guidance document: *Q3D Elemental Impurities*, available at https://www.fda.gov/media/87075/download. In addition, refer to the FDA guidance: Elemental Impurities in Drug Products, available at https://www.fda.gov/media/98847/download.**

7. **All NDA applications filed after June 30, 2015, must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, conduct a thorough review and integrated analysis of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.**

8. **We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity, degradant, or residual solvent that exceeds the recommended qualification thresholds or novel excipients that are not justified for safety.**

Meeting Discussion:
The preliminary comments were found to be adequate. No additional discussion occurred at the meeting.

Additional Discussion:

The Sponsor was asked if they plan to test the ability of kaleo's autoinjector to successfully inject naloxone through Mission Oriented Protective Posture (MOPP) clothing. A DoD representative responded that this testing is being done by the U.S. military and the results would be provided to kaleo in support of an NDA submission.

ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

ACTION ITEMS:

1. The Sponsor should obtain and submit leachables data to support the safety of the higher concentration configuration at the time of NDA submission.

2. The Sponsor should submit the draft protocol with adequate toxicological justification the current existing IND. The Sponsor agreed that the study only can be initiated after they receive an advisory letter to finalize the clinical protocol.

3. Sponsor should submit the human factors study protocol under the IND for Division's review

ATTACHMENTS AND HANDOUTS
Please see attached

7 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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