

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205787Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 205787

SUPPL #

HFD #

Trade Name: Evzio

Generic Name: naloxone hydrochloride injection USP

Applicant Name: Kaleo, Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

#### 505(b)(2)

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

YES  NO

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

The study was a bioavailability study:

**Study IJ-900DV-03O, a randomized, single-dose, single-blind, two sequence, two-period crossover bioavailability, safety and tolerability study in healthy human volunteers. This Phase 1 comparative bioavailability study in healthy volunteers used naloxone hydrochloride (ANDA 072076) supplied by International Medication Systems Limited. (The listed drug, Narcan (NDA 16636) is discontinued and not available for use.)**

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES  NO

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

N/A

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

YES  NO

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

N/A

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

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

YES  NO

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

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

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has

not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

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

NDA# 16636 Narcan

NDA#

NDA#

## 2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

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

To qualify for three years of exclusivity, an application or supplement must contain "reports of new

clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

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

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

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

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



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANA L WALKER  
04/03/2014

BOB A RAPPAPORT  
04/03/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 205787 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Evzio Auto-Injector Established/Proper Name: naloxone hydrochloride USP Dosage Form: injection		Applicant: Kaleo, Inc. Agent for Applicant (if applicable):
RPM: Diana Walker		Division: DAAAP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: April 2, 2014</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>June 20, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR April 3, 2014
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 3/4  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Fast Track            | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review        | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action and date: Approval: April 3, 2014
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Letter: Acceptable: 9/13/2013 Review: 9/13/2013
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None 2/4/2014 DMEPA: <input type="checkbox"/> None 3/27/2014 2/4/2014 12/12/2013 DMPP/PLT (DRISK): <input type="checkbox"/> None 3/28/2014 OPDP: <input type="checkbox"/> None 3/26/2014 SEALD: <input type="checkbox"/> None 3/26/2014 CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None Maternal Health Team: 3/30/2014
Administrative / Regulatory Documents	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	RPM Filing Review: 1/13/2014
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) February 19, 2014
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	

<sup>4</sup> Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP             <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>Date reviewed by PeRC If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	Date of PeRC: 3/5/2014 PeRC Minutes: 3/20/2014  Pediatric Consult Review: 3/30/2014
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	Included
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	1/13/2014 10/2/2013 9/18/2013
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings             <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg Pre-NDA: 6/26/2013 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A PIND: 9/1/2011
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)             <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/2/2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/1/2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None One – 4/1/2014
<b>Clinical</b>	
<ul style="list-style-type: none"> <li>❖ Clinical Reviews             <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No separate review Final: 3/19/2014 Filing: 1/10/2014 <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)</li> </ul>	Included in Clinical review: 3/19/2014
<ul style="list-style-type: none"> <li>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)</li> </ul>	<input type="checkbox"/> None CDRH Devices: 2/19/2014

	CDRH Human Factors: 4/2/2014 CDRH Compliance: 4/1/2014 2/20/2014 1/22/2014
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Final: 3/20/2014 Filing: 1/13/2014
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested Final: 3/11/2014
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Final: 3/20/2014 Filing: 1/10/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Final: 3/21/2013 Filing: 2/10/2014
❖ Microbiology Reviews	<input type="checkbox"/> Not needed Final: 3/7/2013 Filing: /10/2014
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None Compliance Filing: 2/28/2014
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	3/21/2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 4/2/2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done N/A
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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DIANA L WALKER  
04/03/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn](#)  
**Cc:** [Glen Kelley](#); [Brian Riggs](#)  
**Subject:** NDA 205787 Carton and Container comments 28mar14  
**Date:** Friday, March 28, 2014 11:08:48 AM  
**Importance:** High

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Dear Ron,

I have received the following comments from our DMEPA staff regarding the Evzio carton and container labeling. Please review these comments and make the requested changes. Send me the revised carton and container labeling via email as soon as possible. Additionally, please incorporate all previously agreed upon revisions to this carton and container labeling at this time as well. If you do not agree with making the current requested changes, please email me as soon as possible with your points of disagreement, and I will send that on to the review team for discussion.

#### **A. Outer Case Labels**

- 1. Add the statement “Seek Emergency Medical Attention” on the principal display panel to ensure that this important information is visible and helps to prompt the user to seek medical attention. To accommodate this statement, consider shortening the shaft of the arrow or shrinking the arrow overall.**
- 2. The current statement [REDACTED] (b) (4) is inadequately prominent underneath the white highlighted box in the lower third of the principal display panel. Change the statement [REDACTED] (b) (4) to “For opioid emergencies such as overdose”, and consider alternate means for presenting this information (i.e., moving statement up into white highlighted box) to ensure it is easily visible.**

#### **B. Carton Labeling**

- 1. Add the statement “Seek Emergency Medical Attention” on the principal display panel to ensure that this important information is visible and helps to prompt the user to seek medical attention.**
- 2. Change the statement [REDACTED] (b) (4) to “For opioid emergencies such as overdose”, and move the statement “For opioid emergencies such as overdose” from the side panel to the principal display panel for increased prominence.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP

Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
03/28/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@kaleopharma.com\)](mailto:ronald.gunn@kaleopharma.com)  
**Subject:** NDA 205787 PMR Discussion 25mar14  
**Date:** Tuesday, March 25, 2014 1:21:07 PM  
**Importance:** High

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Dear Ron,

Per our discussion via teleconference today, March 25, 2014, propose a PMR study to assess the risk for needle breakage after impact with bone. Additionally, propose a timeline for initiation, completion and submission of the results of this study.

Please send me your proposal via email as soon as possible, followed by an official submission to your NDA this week.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
03/25/2014

**PeRC PREA Subcommittee Meeting Minutes  
March 5, 2014**

**PeRC Members Attending:**

Lynne Yao  
Rosemary Addy  
George Greeley  
Jane Inglese  
Hari Cheryl Sachs  
Wiley Chambers  
Tom Smith  
Peter Starke  
Gregory Reaman  
Daiva Shetty  
Shrikant Pagay  
Lily Mulugeta  
Barbara Buch  
Robert Nelson  
Dianne Murphy

**Agenda**

NDA	205787	Evzio (naloxone hydrochloride autoinjector) (b) (4)	(b) (4)
(b) (4)			

**Evzio (naloxone hydrochloride autoinjector) Partial Waiver**

- NDA 205787 seeks marketing approval for Evzio (naloxone hydrochloride autoinjector) (b) (4)
- The application has a PDUFA goal date of June 30, 2014.
- The application triggers PREA as directed to a new indication and a new dosing regimen.
- (b) (4)
- *PeRC Recommendations:*
  - The Division clarified that the intent of this product is to allow patients, caregivers, and guardians to administer this product when an intentional or unintentional opioid overdose is suspected. This product is being specifically developed to address the public health problems associated with widespread narcotic use/abuse.
  - The PeRC discussed the risks of this product, which include failure to seek follow-up medical care, and breakage of the needle if it hits bone due to the needle length, and discussed whether the benefits outweigh the risks.
  - The PeRC concluded that it is reasonable to label the product now for all populations, but the Division should consider requiring the sponsor to conduct a safety study under FDAAA to ensure that the autoinjector can be used safely in the youngest population.
  - The PeRC also recommended that labeling clearly describe safety concerns related to administration in small infants and children. The PeRC also agreed with the Division’s plan to ensure that labeling clearly state that pediatric patients should seek medical care after administration of the product.



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JANE E INGLESE  
03/20/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@kaleopharma.com\)](mailto:ronald.gunn@kaleopharma.com); [Glen Kelley \(glen.kelley@kaleopharma.com\)](mailto:glen.kelley@kaleopharma.com)  
**Subject:** NDA 205787 DMEPA Information Request 18mar14  
**Date:** Tuesday, March 18, 2014 4:35:58 PM  
**Importance:** High

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Dear Ron,

I have received the following information request for your NDA. Please send me this information as soon as possible via email, followed by a submission to your NDA (can be combined with other submissions if desired). If there is any possibility to receive this information by tomorrow around noon, that would be much appreciated, as we are meeting to continue labeling discussions tomorrow afternoon. If that isn't possible, please send it as soon as it is available.

**We noticed that there have been several iterations of the product's purpose statement used during Human Factors studies, on labels and labeling in the NAI PIL updates 7 24 2012.doc, and on currently proposed labels and labeling. The Human Factors study script included the statements "reverse pain medication overdose" and "pain medication overdose emergency". Whereas the NAI PIL updates label and labeling used the statement [REDACTED] (b) (4), the device samples were labeled with the statement [REDACTED] (b) (4) and recently proposed labels and labeling used the statement [REDACTED] (b) (4). Please provide your data and/or decision process information that was used in making these changes from the initial statement used in HF studies to the most recent statement used in the currently proposed labels and labeling. Specifically, we are interested in what type of decision process and data informed your movement through his process, for example, why earlier purpose statements were discarded in favor of [REDACTED] (b) (4).**

Thank you for your assistance.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
03/18/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@kaleopharma.com\)](mailto:ronald.gunn@kaleopharma.com)  
**Subject:** NDA 205787 Clinical Labeling Information Request 6mar14  
**Date:** Thursday, March 06, 2014 11:43:27 AM  
**Importance:** High

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Dear Ron,

Please provide the following information via email as soon as possible, followed by a submission to your NDA.

**The proposed labeling for your product contains sparse information in the adverse reactions section (i.e., Section 6). To more adequately inform this section of labeling, perform a literature search and characterize the adverse reaction profile specific to naloxone (i.e., not indirect effects such as opioid withdrawal symptoms). Based on this information, propose language formatted and ready for incorporation directly into Section 6, Adverse Reactions, of your product labeling.**

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
03/06/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn](#)  
**Cc:** [Glen Kelley](#); [Brian Riggs](#); [Eric Edwards](#)  
**Subject:** NDA 205787 Clinical-Pediatric Information Request 14feb14 follow-up 03mar14  
**Date:** Monday, March 03, 2014 12:07:15 PM  
**Importance:** High

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Dear Ron,

I have received the following comment/information request related to your preliminary response to our Pediatric Information Request from our review team. Please submit the following requested information to your NDA as soon as possible.

We have reviewed your preliminary response to our Clinical-Pediatric Information Request (dated February 14, 2014) and have the following comments:

Perform a literature search and review on Narcan dosing in pediatrics to support the safety and efficacy of the proposed fixed naloxone dose in Evzio in all pediatric age ranges (i.e., including neonates). Follow this discussion with the already proposed argument for the acceptability of the proposed needle length for Evzio in pediatrics. Then request and propose language for the pediatric section of labeling (i.e., Section 8) based on the aforementioned discussion.

I also remind you that we previously notified you that you should submit copies of all references.

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

---

**From:** Ronald Gunn [<mailto:ronald.gunn@kaleopharma.com>]  
**Sent:** Tuesday, February 18, 2014 3:09 PM  
**To:** Walker, Diana  
**Cc:** Glen Kelley; Brian Riggs; Eric Edwards  
**Subject:** Re: NDA 205787 Clinical-Pediatric Information Request 14feb14

Dear Diana,

Attached is a preliminary response to the Clinical-Pediatric Information Request received on

14Feb2014. Please forward this email and attached response to the clinical/pediatric review teams for their consideration. If necessary, we would like to hold a teleconference with the clinical/pediatric reviewers to ensure alignment prior to formally amending the NDA.

We will begin preparing the formal submission to NDA 205,787 in parallel to FDA's informal review.

**Would it be helpful to FDA if we include copies of all references cited in the enclosed response** (b) (4)  
**\_\_\_\_\_**  
**\_\_\_\_\_ in the formal submission to NDA 205,787?**

Please let us know if you have additional suggestions for how we might further facilitate FDA's review of this information.

With sincere regards,

Ron  
Ronald D. Gunn  
Vice President, Drug Development & Regulatory Affairs

**kaléo**  
111 Virginia Street, Suite 300  
Richmond, VA 23219

(Office)  
804.545.6376  
(Mobile)  
\_\_\_\_\_  
(b) (6)  
(Fax)  
804.545.6219

[www.kaleopharma.com](http://www.kaleopharma.com)

Note my new email address is [ronald.gunn@kaleopharma.com](mailto:ronald.gunn@kaleopharma.com) and the company's website is [www.kaleopharma.com](http://www.kaleopharma.com)

On Feb 18, 2014, at 9:36 AM, Walker, Diana <[Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)> wrote:

I think that in this case, since it is essentially a revision of your pediatric proposal/plan, it would be best to submit this to the Pediatric section.

Regards,

Diana

---

**From:** Ronald Gunn [<mailto:ronald.gunn@kaleopharma.com>]  
**Sent:** Friday, February 14, 2014 4:29 PM  
**To:** Walker, Diana

**Cc:** Glen Kelley; Brian Riggs

**Subject:** Re: NDA 205787 Clinical-Pediatric Information Request 14feb14

**Importance:** High

Dear Diana,

Does FDA have a preference for which eCTD section we submit our formal response into: Section 1.11 Response to FDA Request for Information or Section 1.9 Pediatric Administrative Information?

Thanks,

Ron

On Feb 14, 2014, at 1:47 PM, Walker, Diana <[Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)> wrote:

Dear Ron,

Please provide the following justification, literature, and data as soon as possible (you can send this via email initially, but it must be submitted officially to your NDA as well).

**Given the safety margin for naloxone, the clinical consequences of not treating an opioid overdose, and that it would not be practical to deliver pediatric weight-based dosing for naloxone (as is currently recommended in the Narcan labeling) in a community setting, we are inclined to believe that your product containing a 0.4 mg fixed dose of naloxone would be appropriate for all pediatric age ranges. Therefore, you may wish to approach addressing the requirements under PREA by providing a justification (e.g., from literature, approved Narcan labeling) for why your product containing a fixed dose of naloxone is acceptable for all pediatric age ranges so as to inform pediatric labeling for your product. Also, as part of this justification, you must provide data for why the needle length in your product is acceptable for all pediatric age ranges (i.e., to deliver the dose subcutaneously or intramuscularly, and will not strike bone).**

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

Ronald D. Gunn

Vice President, Drug Development & Regulatory Affairs

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[www.kaleopharma.com](http://www.kaleopharma.com)

Note my new email address is [ronald.gunn@kaleopharma.com](mailto:ronald.gunn@kaleopharma.com) and the company's website is [www.kaleopharma.com](http://www.kaleopharma.com)

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[ronald.gunn@kaleopharma.com](mailto:ronald.gunn@kaleopharma.com)

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DIANA L WALKER  
03/03/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@kaleopharma.com\)](mailto:ronald.gunn@kaleopharma.com)  
**Subject:** NDA 205787 Microbiology Information Request 27feb14  
**Date:** Thursday, February 27, 2014 10:11:43 AM  
**Importance:** High

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Dear Ron,

I have receive the following request for information from our microbiology review team  
Please submit a response to the following information request as soon as possible, or no  
later than next week.

**The submitted labeling indicates that this product may be used [REDACTED] (b) (4)**  
[REDACTED] **The current endotoxin limit of [REDACTED] (b) (4) EU/mg complies with the USP<85> recommended  
maximum dose of 5 EU/kg/hr for patients weighing 40 kg or greater. The results from stability  
studies demonstrate endotoxin levels < [REDACTED] (b) (4) EU/mg. To prevent potential pyrogenic reactions in  
infants, revise the endotoxin limit to ≤ [REDACTED] (b) (4) EU/mg naloxone.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
02/27/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@kaleopharma.com\)](mailto:ronald.gunn@kaleopharma.com)  
**Subject:** NDA 205787 DMEPA Comments/Information Request 19Feb2014  
**Date:** Wednesday, February 19, 2014 5:35:34 PM  
**Importance:** High

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Dear Ron,

I have received the following comments from our DEMPAs review team regarding your labeling. Please note that it is possible that there could be an additional comment(s) regarding the carton and container, but these comments are being sent to you now in order to provide you with feedback as soon as possible. Also, we will definitely be sending comments separately regarding your Package Insert labeling in the future, hopefully near to or before mid-March. Please respond to the following recommendations:

**A. General Comments for all Labels and Labeling**

1. We do not agree with your proposal (b) (4) (b) (4) on the outer case or carton labeling. Per the Office of New Drug Quality Assessment (ONDQA), the established name should appear as designated in the USP monograph on all labels and labels as "naloxone hydrochloride injection, USP". (b) (4)  
Additionally, inconsistent use of an established name throughout labels and labeling may be a source of confusion. Alternatively, we would find it acceptable to use "naloxone HCl injection, USP" (b) (4)

**B. Carton Labeling for the (b) (4)**

1. Remove the statement "(b) (4)"  
Instead, increase the font of the statement "For Practice Only".

2. The proprietary name Evzio on the principal display panel is overly prominent and should be revised so it is the same font size and type as the word "for" immediately preceding it.

Warm regards.

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
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DIANA L WALKER  
02/19/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@kaleopharma.com\)](mailto:ronald.gunn@kaleopharma.com)  
**Subject:** NDA 205787 Clinical-Pediatric Information Request 14feb14  
**Date:** Friday, February 14, 2014 1:47:38 PM  
**Importance:** High

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Dear Ron,

Please provide the following justification, literature, and data as soon as possible (you can send this via email initially, but it must be submitted officially to your NDA as well).

**Given the safety margin for naloxone, the clinical consequences of not treating an opioid overdose, and that it would not be practical to deliver pediatric weight-based dosing for naloxone (as is currently recommended in the Narcan labeling) in a community setting, we are inclined to believe that your product containing a 0.4 mg fixed dose of naloxone would be appropriate for all pediatric age ranges. Therefore, you may wish to approach addressing the requirements under PREA by providing a justification (e.g., from literature, approved Narcan labeling) for why your product containing a fixed dose of naloxone is acceptable for all pediatric age ranges so as to inform pediatric labeling for your product. Also, as part of this justification, you must provide data for why the needle length in your product is acceptable for all pediatric age ranges (i.e., to deliver the dose subcutaneously or intramuscularly, and will not strike bone).**

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
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DIANA L WALKER  
02/14/2014

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@kaleopharma.com\)](mailto:ronald.gunn@kaleopharma.com)  
**Subject:** NDA 205787 CDRH Device Information Request 14feb14  
**Date:** Friday, February 14, 2014 8:47:42 AM  
**Importance:** High

---

Dear Ron,

Please provide the following information as soon as possible, or by February 20, 2014.

We are missing a vital piece of information, which is the dose accuracy test results, to show how accurately the naloxone autoinjector can deliver the 0.4ml of naloxone. Clarify whether that result is embedded elsewhere in the electronic submission (not under 3.2.p.7). If yes, provide the date of submission, sequence number and section number. If no, submit the information by the date requested above.

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
02/14/2014

**From:** Walker, Diana  
**To:** Ronald Gunn (ronald.gunn@kaleopharma.com)  
**Subject:** NDA 205787 Microbiology Information Request 24jan14  
**Date:** Friday, January 24, 2014 10:39:48 AM  
**Importance:** High

---

Dear Ron,

I have received the following requests for information from our Microbiology review team. Please submit a response to the following requests for information to your NDA as soon as possible.

**Provide the following information or a reference to its location in the application.**

1. Justify the conduct of integrity testing for the cartridge assembly on product that had not been subjected to (b) (4).

2. We refer to document IJ-705R-03O-02 section 6 deviations. Describe the (b) (4) that were referenced in IS02651.

3. The sterile needle should be (b) (4) and no information was found in the NDA regarding (b) (4) of the needle. Describe the (b) (4) for the (b) (4) needle.

4. We refer to the 2012 and 2013 (b) (4) validation reports 21TJ1-12V1) and 21TJ1-13V1.

a. We note your reference to the 2008 original validation studies conducted for the epinephrine autoinjector. Confirm that no major changes were made to the (b) (4) that were validated for the epinephrine autoinjector manufactured by Intelliject. We note reference to changes to the (b) (4) in section III but no data were provided to verify that these changes did not impact the (b) (4).

b. Describe the study and results from the (b) (4). Clearly indicate how this surrogate provides equivalent, or worst-case, results in lethality studies conducted with biological indicators.

c. Provide (b) (4) used to evaluate the test and (b) (4).

d. The results from residuals testing on the cartridge contents in the NDA are expressed in mg and should be expressed in parts per million. CDER uses the limits proposed in the 1978 Federal Register, which may be found here

(<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM078413.pdf>). The residuals for the liquid cartridge components should be < (b) (4) ppm (b) (4), < (b) (4) ppm (b) (4), and < (b) (4) ppm (b) (4). Submit the results from validation studies that demonstrate that the proposed aeration time is adequate to meet these limits in the drug product.

e. We note your statement that there are no required limits for (b) (4) for the cartridge contents. Provide a scientific basis for this omission or revise the specification to require testing for (b) (4).

f. Justify the lack of data for (b) (4) residuals for the needle assembly.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER  
01/24/2014



NDA 205787

**DISCIPLINE REVIEW LETTER**

Kaleo, Inc.  
111 Virginia Street  
Suite 405  
Richmond, VA 23219

Attention: Ronald D. Gunn  
V.P., Drug Development and Regulatory Affairs

Dear Mr. Gunn:

Please refer to your New Drug Application (NDA) received December 20, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Naloxone autoinjector (NAI).

We also refer to your amendments dated July 18 (2), August 23, September 13 and 27, October 10, 22, and 29, November 22, and December 11 and 31, 2013, and January 2, 3, 13, and 20, 2014.

The Center for Devices and Radiological Health (CDRH), Office of Compliance has completed their review of your submission, and has identified the following deficiencies with the Kaleo/Intelliject documents:

1. Document controls, 21 CFR820.40 requirements  
All procedures and documents provided to show compliance with the regulatory requirements under 21 CFR part 820 should be updated to reflect the firm's name change from Intelliject to Kaleo.

(b) (4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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PARINDA JANI  
01/22/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 205787

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Kaleo, Inc.  
111 Virginia Street  
Suite 405  
Richmond, VA 23219

Attention: Ronald D. Gunn  
V.P., Drug Development and Regulatory Affairs

Dear Mr. Gunn:

Please refer to your New Drug Application (NDA) received December 20, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Naloxone autoinjector (NAI).

We also refer to your amendments dated July 18 (2), August 23, September 13 and 27, October 10, 22, and 29, November 22, and December 11 and 31, 2013, and January 2, 3, 13, and 20, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 20, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 30, 2014.

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

**Clinical**

We note that you have submitted integrated summary information (i.e., efficacy and safety) in the clinical overview and clinical summary sections. However, you must cross-reference this information in Module 5.3.5.3 (i.e., the integrated summary of safety [ISS] and integrated summary of effectiveness [ISE]).

**Product Quality**

1. Batch data and stability data do not support the proposed specifications noted in the related substances of the drug product, which are higher than those noted in the related substances in the drug substance, at release and on stability. Tighten the specifications or provide adequate justification for the higher limits proposed in the drug product.
2. Clarify the data entry for "Total Impurities" in Table 3.2.P.5.4.3., Batch Analysis of the Drug Product, which lists the total impurities as NMT <sup>(b) (4)</sup>% when all of the controlled impurities are all at or below the LOQ.
3. Explain why, in Table 3.2.P.5.4.4 Batch Analysis of the Drug Product, testing for two impurities was not implemented.

**Microbiology**

1. We refer to your October 10, 2013, submission that contained copies of validation studies (5020499, 5025674, and 5026878) conducted for each of the three proposed equipment <sup>(b) (4)</sup>. The validation approach utilized by <sup>(b) (4)</sup> laboratories is not consistent with industry practices and more information is needed to evaluate the validation studies. Provide the following information or a reference to its location in the NDA.

a. <sup>(b) (4)</sup>

b. The following is stated in Module 3.2.P.5.2.3 page 4/16, <sup>(b) (4)</sup>  
<sup>(b) (4)</sup>  
<sup>(b) (4)</sup> Describe the specific circumstances when the <sup>(b) (4)</sup> provide the results from those studies.

- c. Include a description of the temperature and biological monitoring points used for (b) (4) We note your submission (b) (4)
  - d. Provide a detailed summary or a copy of the EPL PAK documents (e.g., EPL PAK 3, 4, 5) used to define the loads used in the three (b) (4) studies.
  - e. (b) (4)
  - f. The table in section 11.4 of report 5025674 appears to contain an error. The acceptance criteria require (b) (4) to (b) (4) mm:ss in the range of (b) (4) to (b) (4) C. The results indicate that the actual time was (b) (4) mm:ss and this was considered acceptable. Please explain this discrepancy.
2. We refer to the cartridge (b) (4) studies described in document 5016832. The studies do not contain sufficient details to allow evaluation of the proposed (b) (4) process. Provide the following information:

(b) (4)

(b) (4)

(b) (4)

3. Justify the conduct of sterility testing prior to assembly of the final drug product.

Specifically, address the risk for loss of container integrity

(b) (4)

(b) (4)

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

### **PROMOTIONAL MATERIAL**

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

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

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your [REDACTED] <sup>(b) (4)</sup> for this application.  
Once we have reviewed your request, we will notify you if [REDACTED] <sup>(b) (4)</sup> a  
pediatric drug development plan is required.

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

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, MD  
Director  
Division of Anesthesia, Analgesia and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BOB A RAPPAPORT  
01/22/2014

**From:** Walker, Diana  
**To:** ["Ronald Gunn"](#)  
**Cc:** ["Glen Kelley"](#); ["Brian Riggs"](#)  
**Subject:** Follow-up - RE: NDA 205787 Compliance Information Request 14Jan14  
**Date:** Wednesday, January 15, 2014 11:13:00 AM  
**Importance:** High

---

Dear Ron,

I have a follow-up clarification concerning our request sent to you yesterday. The information request sent yesterday applies specifically to these two facilities:

1. Kaleo (FEI # 3007135538)  
111 Virginia Street, Suite 300  
Richmond, VA 23229

2.  (b) (4)

Please respond with your clarification regarding both facilities.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

---

**From:** Walker, Diana  
**Sent:** Tuesday, January 14, 2014 5:53 PM  
**To:** 'Ronald Gunn'  
**Cc:** Glen Kelley; Brian Riggs  
**Subject:** NDA 205787 Compliance Information Request 14Jan14  
**Importance:** High

Dear Ron,

I have received a request for clarification from our CDRH Compliance review team as to whether you have declared a QS system. Please clarify the following:

**We request clarification regarding your compliance with all applicable good manufacturing regulations as required in 21 CFR part 4. Explicitly, we need to know if you are taking advantage of 21 CFR 4.4(b), and if so, whether you will be following 4.4(b)(1) or 4.4(b)(2).**

FYI: below is that section of the final rule for your information. Section 4.4(b) speaks of how applicants can show compliance with the applicable QS regulations.

**§ 4.4 How can I comply with these current good manufacturing practice requirements for a co-packaged or single-entity combination product?**

(a) Under this subpart, for single entity or co-packaged combination products, compliance with all applicable current good manufacturing practice requirements for the combination product shall be achieved through the design and implementation of a current good manufacturing practice operating system that is demonstrated to comply with:

(1) The specifics of each set of current good manufacturing practice regulations listed under § 4.3 as they apply to each constituent part included in the combination product; or

(2) Paragraph (b) of this section.

(b) If you elect to establish a current good manufacturing practice operating system in accordance with paragraph (b) of this section, the following requirements apply:

(1) If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug CGMPs, the following provisions of the QS regulation must also be shown to have been satisfied; upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QS regulation need be made:

(i) Section 820.20 of this chapter. Management responsibility.

(ii) Section 820.30 of this chapter. Design controls.

(iii) Section 820.50 of this chapter. Purchasing controls.

(iv) Section 820.100 of this chapter. Corrective and preventive action.

(v) Section 820.170 of this chapter. Installation.

(vi) Section 820.200 of this chapter. Servicing.

(2) If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the QS regulation, the following provisions of the drug CGMPs must also be shown to have been satisfied; upon

demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the drug CGMPs need be made:

(i) Section 211.84 of this chapter.

Testing and approval or rejection of components, drug product containers, and closures.

(ii) Section 211.103 of this chapter.

Calculation of yield.

(iii) Section 211.132 of this chapter.

Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(iv) Section 211.137 of this chapter.

Expiration dating.

(v) Section 211.165 of this chapter.

Testing and release for distribution.

(vi) Section 211.166 of this chapter.

Stability testing.

(vii) Section 211.167 of this chapter.

Special testing requirements.

(viii) Section 211.170 of this chapter.

Reserve samples.

(3) In addition to being shown to comply with the other applicable manufacturing requirements listed under § 4.3, if the combination product includes a biological product constituent part, the current good manufacturing practice operating system must also be shown to implement and comply with all manufacturing requirements identified under § 4.3(c) that would apply to that biological product if that constituent part were not part of a combination product.

(4) In addition to being shown to comply with the other applicable current good manufacturing practice requirements listed under § 4.3, if the combination product includes an HCT/P, the current good manufacturing practice operating system must also be shown to implement and comply with all current good tissue practice requirements identified under § 4.3(d) that would apply to that HCT/P if it were not part of a combination product.

(c) During any period in which the manufacture of a constituent part to be included in a co-packaged or single entity combination product occurs at a separate facility from the other constituent part(s) to be included in that single-entity or co-packaged combination product, the current good manufacturing practice operating system for that constituent part at that

facility must be demonstrated to comply with all current good manufacturing practice requirements applicable to that type of constituent part.

(d) When two or more types of constituent parts to be included in a single-entity or co-packaged combination product have arrived at the same facility, or the manufacture of these constituent parts is proceeding at the same facility, application of a current good manufacturing process operating system that complies with paragraph (b) of this section may begin.

(e) The requirements set forth in this subpart and in parts 210, 211, 820, 600 through 680, and 1271 of this chapter listed in § 4.3, supplement, and do not supersede, each other unless the regulations explicitly provide otherwise. In the event of a conflict between regulations applicable under this subpart to combination products, including their constituent parts, the regulations most specifically applicable to the constituent part in question shall supersede the more general.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
01/15/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: January 13, 2014

TO: Director, Investigations Branch  
Baltimore District Office  
6000 Metro Dr., Suite 101  
Baltimore, MD 21215

Director, Investigations Branch  
Minneapolis District Office  
250 Marquette Ave., Suite 600  
Minneapolis, MN 55401

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER PDUFA, High Priority Pre-Approval Data  
Validation Inspection**, Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 205-787  
DRUG: Naloxone Autoinjector, 0.4 mg  
SPONSOR: Kaleo Inc., USA

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence (BE) study.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo to schedule the inspection of the analytical site. A DBGLPC scientist will participate in the inspection of the analytical site to provide scientific and technical expertise.

Background materials will be available in ECMS under the ORA folder. **The inspections should be completed prior to March 15, 2014.**

**Do not reveal the applicant, application number, study to be inspected, drug name, or the study investigators to the sites prior to the start of the inspections.** The sites will receive

this information during the inspection opening meeting. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

**At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.**

**Study:** IJ-900DV-030  
**Study Title:** "A Randomized, Single-Blind, Two-Sequence, Two-Period Comparative Bioavailability Study of Two Naloxone Hydrochloride Products in Healthy Human Volunteers"

**Clinical Site:** PAREXEL Early Phase Clinical Unit  
Harbor Hospital, 7th Floor  
3001 South Hanover Street  
Baltimore, Maryland 21225

**Investigator:** Dr. Ronald Goldwater  
TEL: 410-350-7979  
FAX: 410-350-4281

#### **SECTION A - RESERVE SAMPLES**

Because this bioequivalence study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the Applicant for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

**During the clinical site inspection, please:**

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the DBGLPC POC immediately.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.  
Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
645 S. Newstead Ave  
St. Louis, MO 63110  
TEL: 1-314-539-2135

#### **SECTION B - CLINICAL DATA AUDIT**

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

#### **During the clinical site inspection, please:**

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.
- Compare the study report in the NDA submission to the original documents at the site.
- Check for under-reporting of adverse events (AEs).

- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
  - o Number of subject records reviewed during the inspection:\_\_\_\_\_
  - o Number of subjects screened at the site:\_\_\_\_\_
  - o Number of subjects enrolled at the site:\_\_\_\_\_
  - o Number of subjects completing the study:\_\_\_\_\_
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**SECTION C - AUDIT OF ANALYTICAL DATA**

**Analytical Site:**

(b) (4)

**Contact person:**

**Methodology:**

LC-MS/MS

**During the analytical site inspection, please:**

- Examine all pertinent items related to the analytical method used for the measurement of naloxone concentrations in human plasma.
- Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- Determine if the site employed a validated analytical method to analyze the subject samples.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.
- Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.
- Examine correspondence files between the analytical site and the Applicant for their content.

**Additional instructions to the ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

**If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.**

**Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the DBGLPC POC.**

DBGLPC POC: Chase Bourke, Ph.D.  
Pharmacologist  
Office of Scientific Investigations  
Tel: 1-240-402-4129  
Fax: 1-301-847-8748  
E-mail: [chase.bourke@fda.hhs.gov](mailto:chase.bourke@fda.hhs.gov)

DARRTS cc:  
CDER OSI PM TRACK  
OSI/DBGLPC/Taylor/Bonapace/Haidar/Mada/Bourke/Dejernet  
CDER/OND/Walker  
CDER/OTS/OCP/Xu/Qiu

Email cc:  
ORA DO/Richard-Math/Harris/Smith/Armendariz

Draft: CHB 01/06/2014  
Edit: SRM 01/08/2014  
ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ (b) (4)  
ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Parexel, Baltimore, MD  
OSI file # BE6660  
**FACTS:** 8742520

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/s/  
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CHASE H BOURKE  
01/13/2014

CHARLES R BONAPACE  
01/13/2014

## Rivera, Luz E (CDER)

---

**From:** Rivera, Luz E (CDER)  
**Sent:** Thursday, January 02, 2014 11:46 AM  
**To:** 'ronald.gunn@intelliject.com'  
**Subject:** NDA 205787

Good morning Mr. Gunn,

We are reviewing your New Drug Application # 205787 and request additional information to continue our evaluation.

- Specify the quality control testing to be performed at the following facilities:
  1.  (b) (4)
  2. 
  3. 
  4. 
- Clarify if the  (b) (4) listed in the application is a manufacturing facility or administrative building?

Submit the information requested by email to me ([Luz.E.Rivera@fda.hhs.gov](mailto:Luz.E.Rivera@fda.hhs.gov))

Please acknowledge the receipt of this request

Thank you,  
Luz E Rivera, Psy.D.  
LCDR, US Public Health Service  
Regulatory Health Project Manager  
FDA/CDER/OPS/ ONDQA  
Division of New Drug Quality Assessment III  
[luz.e.rivera@fda.hhs.gov](mailto:luz.e.rivera@fda.hhs.gov)  
301 796 4013

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/s/  
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LUZ E RIVERA  
01/09/2014



NDA 205787

**NDA ACKNOWLEDGMENT  
TRANSFER OF NDA OWNERSHIP**

Kaleo, Inc.  
111 Virginia Street  
Suite 405  
Richmond, VA 23219

Attention: Ronald D. Gunn  
V.P., Drug Development and Regulatory Affairs

Dear Mr. Gunn:

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

Name of Drug Product: Naloxone autoinjector (NAI)

Date of Application: December 20, 2013

Date of Receipt: December 20, 2013

Our Reference Number: NDA 205787

We also acknowledge the receipt of your December 20, 2013, correspondence notifying the Food and Drug Administration of the change of ownership of NDA 205787:

Name of New Applicant: Kaleo, Inc.

Name of Previous Applicant: Intelliject VA, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Kaleo, Inc., as the applicant of record for this application.

## **DRUG MASTER FILE LOA**

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s) and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **February 18, 2014**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and

submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 205787** submitted on December 20, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

*{See appended electronic signature page}*

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

Cc: Intelliject VA, Inc.  
111 Virginia Street  
Suite 405  
Richmond, VA 23219

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/s/  
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DIANA L WALKER  
12/24/2013

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@intelliject.com\)](mailto:ronald.gunn@intelliject.com)  
**Subject:** NDA 205787 Labeling Information Request 24dec13  
**Date:** Tuesday, December 24, 2013 2:44:52 PM  
**Importance:** High

---

Dear Ron,

I am in the process of reviewing your NDA submission in total (all submissions of the rolling submission, up to and including your final submission dated December 20, 2013) in terms of administrative documents and information, and have the following requests so far. Request #2 and #3 are also included in the NDA Acknowledgement letter you will be receiving soon, but I am including them here so that you will receive our information requests as soon as possible. Submit all of these items to your NDA as soon as possible, but please submit Item #1 to your NDA by January 3, 2014.

1. You did not submit proposed package insert (USPI) labeling to your NDA.

We refer to the requirements on content and format of labeling for human prescription drug and biological products. These requirements are also referred to as the Physician Labeling Rule (PLR). Please refer to the following website for additional information:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

Submit draft labeling in PLR format to your pending NDA 205787. Include the proposed Package Insert in PLR format as both a **Word document** and as a PDF.

2. Promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

3. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)]. You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
12/24/2013

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn \(ronald.gunn@intelliject.com\)](#)  
**Cc:** [Glen Kelley \(glen.kelley@intelliject.com\)](#); [Brian Riggs \(brian.riggs@intelliject.com\)](#)  
**Subject:** NDA 205787 Labeling Comments 12dec13  
**Date:** Thursday, December 12, 2013 4:40:39 PM

---

Dear Ron,

I am sending comments from DMEPA regarding some of the components of the labeling for NDA 205787. Note that we are not sending comments on the USPI at this time.

A. General Comments for all Labels and Labeling

1. Ensure that the proprietary name and the approved USAN established name are the most prominent information on the label.

B. Evzio Device Label

1. Summative study results showed that critical use errors occurred related to pressing and holding the device against the patient's injection location. Therefore, we recommend that you revise all words to title case to improve readability and relocate the "Makes CLICK and HISS SOUND during injection" statement to appear beneath the graphic of the outer thigh (second instruction) box so that end users know what to expect when administering an injection, since at least two summative study participants did not press hard enough to activate and one of them mentioned that she didn't know she had to press it until it clicked.

C. Trainer Label and Trainer Outer Case Label

1. Summative study results showed that critical use errors occurred related to selection of the Trainer device instead of the NAI Study device. Therefore, we recommend that you revise the name from (b) (4) to "TRAINER for Evzio" as the word "Trainer" is the most important differentiating word for the names of the devices and may help to mitigate error of wrong device selection.

D. Evzio Device Outer Case Label

1. Add the storage information statement "Store at room temperature" to the side panel before the "Do not Refrigerate or Freeze" statement.

E. Carton Labeling

1. Summative study results showed that critical use errors occurred related to incorrect device selection. When the trainer is mistaken for the drug device, this could present a serious risk if a trainer is used in an urgent circumstance. It does not appear that you have mitigated this risk. To further differentiate the two devices containing drug from the trainer device, we recommend that you consider revising the packaging configuration to separate the devices containing drug from the trainer device by:

a. having one carton for device containing drug and one carton for the trainer device

- b. providing a physical barrier between the two within the packaging, or
- c. providing an additional primary carton for the trainer similar to Auvi-Q that bears the statement on the principal display, side and back panels “Trainer for Evzio contains no active drug or needle”.

2. See D 1 above.

3. The net quantity of device units is not provided on the carton. Revise the net quantity statement by providing the total number of devices to read as follows: “This carton contains three units: two Evzio Auto-Injectors and one Trainer”.

F. Evzio Information and Instructions for Use

1. Remove the bulleted sentence that starts with [REDACTED] (b) (4) and the corresponding graphic (Figure 1) as this symptom is not exclusive to opioid overdose.

G. Trainer Information and Instructions for Use

1. Summative study results showed that critical use errors occurred related to selection of the Trainer device instead of the NAI Study device, therefore we recommend to revise the title and any reference throughout from [REDACTED] (b) (4) to “TRAINER for Evzio” as the word “Trainer” is the most important differentiating word for the names of the devices and may help to mitigate confusion and error of wrong device selection.

2. Revise all references to Evzio from [REDACTED] (b) (4) to “Evzio” for consistency with the Evzio Information and Instructions for Use and use of the proper proprietary name.

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: Diana.Walker@fda.hhs.gov

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DIANA L WALKER  
12/13/2013

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn](#)  
**Cc:** [Glen Kelley](#); [Brian Riggs](#)  
**Subject:** NDA 205787 Clinical Pharmacology Information Request 06Nov13  
**Date:** Wednesday, November 06, 2013 11:45:27 AM  
**Importance:** High

---

Dear Mr. Gunn,

I have received an information request from our clinical pharmacology review team. Please submit the requested information to your NDA 205787.

**Regarding your PK study IJ-900DV-030, we did not find information on how many subjects received subcutaneous (SC) or intramuscular (IM) injection with either your product or the reference product, although you indicated in your study report that these products are given IM or SC.**

- 1. Submit information on the number of subjects that received IM or SC injection using your product or the reference product.**
- 2. Provide a summary table showing the PK comparison of your product versus the reference product following IM or SC administration.**
- 3. Resubmit datasets with PK raw data and PK parameters, adding a column for route of administration (SC or IM). These datasets should be ready for analysis using WinNonlin.**

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
11/06/2013



NDA 205787

**ACKNOWLEDGE TRANSFER NDA OWNERSHIP**

Intelliject VA, Inc.  
111 Virginia Street, Suite 405  
Richmond, VA 23219

Attention: Ronald D. Gunn  
V.P., Drug Development and Regulatory Affairs

Dear Mr. Gunn:

We acknowledge the October 10, 2013, receipt of your October 8, 2013, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: Naloxone autoinjector (NAI)

NDA Number: 205787

Name of New Applicant: Intelliject VA, Inc.

Name of Previous Applicant: Intelliject, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Intelliject VA, Inc. as the applicant of record for this application.

**DRUG MASTER FILE LOA**

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s) and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

**REPORTING REQUIREMENTS**

All changes to the information in the NDA from that described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. However, changes in the name of the manufacturer, packer, or distributor in the drug product's label or labeling may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 21 CFR 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

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

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

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

*{See appended electronic signature page}*

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

CC:  
Intelliject, Inc.  
111 Virginia Street, Suite 405  
Richmond, VA 23219

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DIANA L WALKER  
10/25/2013

**From:** Walker, Diana  
**To:** [Ronald Gunn \(ronald.gunn@intelliject.com\)](mailto:Ronald.Gunn@intelliject.com)  
**Subject:** NDA 205787 DMEPA Information Request 11Oct 13  
**Date:** Friday, October 11, 2013 3:30:00 PM

---

Dear Ron,

I have received a request for information from our DMEPA review team. Please submit the following information to your NDA.

**Clarify if the Information and Instructions for Use (IFU) leaflets (for the both the device and the trainer) submitted July 19, 2013, were intended to be presented in a 3 column per page format like the excerpt from the draft IFU provided in section 8.6.3 of the human factors study report on page 34 or in a one column per page format as submitted July 19, 2013? Please submit the correct version for our review.**

Warm regards.

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
10/11/2013

**From:** [Walker, Diana](#)  
**To:** ["Ronald Gunn"](#)  
**Cc:** ["Glen Kelley"](#); ["Brian Riggs"](#)  
**Subject:** NDA 205787 Information Request 10Oct13  
**Date:** Wednesday, October 09, 2013 11:11:13 AM  
**Importance:** High

---

Dear Mr. Gunn,

I have received an information request from our OSE and clinical review teams. Please submit the requested information to your NDA 205787.

**Regarding your submission #3 to NDA 205787, dated August, 23, 2013, FDA requests that you re-submit your literature review to include additional information.**

**Specifically, provide the following for EACH risk factor that was identified in section 2 of the integrated summary:**

- 1) Provide a summary table of citation(s) that identify the literature supporting the specific risk factor.**
- 2) Provide a summary table in the literature review to allow for a critique of the quality of evidence that was cited as identifying the specific risk factor. Each table must include the following key elements depending on the type of literature reviewed:**
  - a. For literature reporting formal studies (clinical trials, observational studies, etc.):**
    - Study objective
    - Study design
    - Data source
    - Population
    - Sample size
    - Outcome definition
    - Risk factor definition
    - Covariate(s) definition
    - Analytical approach
    - Main findings on the identified risk factor
    - Study strengths and limitations related to the identified risk factor
  - b. For literature reporting expert consensus on risk factors (i.e. guidelines):**
    - Type of opioid
    - Indication
    - Targeted patient population
    - Rationale to support the risk factor
    - Level of evidence to support the risk factor
    - Recommendations, if any

**For any systematic review of the literature, unless the systematic review provides the above information to critique evidence quality, we encourage you to search for the original article(s) instead of citing the systematic review and provide a table of the bulleted information in 2a or 2b, depending on the nature of the literature report.**

- 3) **Provide a summary table to facilitate the understanding of the magnitude of the specific risk factor. This table should include the observed risk estimates (e.g., risk ratio, or rate ratio) from all the studies that identified the risk factor.**
- 4) **Provide estimations of the number of persons with each risk factor that would be needed to treat (NNT) with NAI to prevent one opioid overdose. If such estimation is not feasible for a risk factor, you must specify the missing information preventing the calculation of the NNT.**
- 5) **Additionally, explain how the risk factors selected and listed in the annotated Package Insert were identified from the larger number of risk factors identified in the literature review.**

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
10/09/2013

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn](#)  
**Cc:** [Glen Kelley](#); [Brian Riggs](#)  
**Subject:** NDA 205787 Voice Prompt Script 02Oct13  
**Date:** Wednesday, October 02, 2013 2:29:49 PM

---

Dear Mr. Gunn,

I have received the following comment concerning your voice prompt script:

**We have reviewed the voice instruction prompt script for the Naloxone Auto Injector trainer and delivery devices submitted by Intelliject, Inc. on July 19, 2013, to NDA 205787. We find the voice instruction prompt script to be acceptable.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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DIANA L WALKER  
10/02/2013

**From:** [Nguyen, Quynh Nhu](#)  
**To:** [Walker, Diana](#)  
**Subject:** RE: Voice Message from Walker, Diana (83017964029)  
**Date:** Wednesday, October 02, 2013 2:22:33 PM

---

Yes, from CDRH HF's review perspective, we have no concerns on the voice prompt in particular or any other user interface associated with the NAI in general.

---

**From:** Walker, Diana  
**Sent:** Wednesday, October 02, 2013 2:21 PM  
**To:** Nguyen, Quynh Nhu  
**Subject:** RE: Voice Message from Walker, Diana (83017964029)

Q,

Thanks, that's great. Would I be safe to send the Sponsor comments on the voice prompt before you finalize the memo (that we have no concerns)? Since DMEPA also had no concerns on the voice prompt, I thought I would send that to the Sponsor right away. DMEPA is still finalizing review of the labeling on the device, so I won't send comments on that yet.

Thanks,

Diana

---

**From:** Nguyen, Quynh Nhu  
**Sent:** Wednesday, October 02, 2013 2:12 PM  
**To:** Walker, Diana  
**Subject:** RE: Voice Message from Walker, Diana (83017964029)

Diana,

Sorry for the delay. Had to respond to several priorities. I did review the HF report and did not have any concerns regarding the voice prompt or any other user interface associated with the NAI product. I will get you a finalized memo soon.

Q-

**From:** Walker, Diana  
**Sent:** Wednesday, October 02, 2013 11:33 AM  
**To:** Nguyen, Quynh Nhu  
**Subject:** Voice Message from Walker, Diana (83017964029)

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DIANA L WALKER  
10/02/2013

**From:** [Walker, Diana](#)  
**To:** ["Ronald Gunn"](#)  
**Cc:** ["Glen Kelley"](#); ["Brian Riggs"](#)  
**Subject:** NDA 205787 Microbiology Information Request 26sep13  
**Date:** Thursday, September 26, 2013 3:17:30 PM  
**Importance:** High

---

Dear Mr. Gunn,

I have received an information request from our Microbiology review team. Please submit the requested information to your NDA 205787.

1. **Provide a description of and a summary of the results from the sterility and endotoxin method verification studies for the drug product constituent (Naloxone hydrochloride).**
2. **Provide a description of and a summary of the results from (b) (4) validation studies for the drug constituent manufacturing process. Include:**



3. **Provide a description of the media and incubation conditions for the environmental monitoring program.**
4. **Define x in table 3.2.P.3.5.3-12.**
5. **Indicate the number of filling lines in Clean Room (b) (4).**
6. **Provide a description of the (b) (4) and the initial qualification run dates.**
7. **Provide the following information for the (b) (4) used to support Naloxone manufacture:**
  - a. **The number of units filled**
  - b. **The number of units rejected, with a brief explanation of the reason for the rejection**
  - c. **The number of units incubated**
  - d. **The number of positive units**
  - e. **The line speed**
  - f. **The container closure system used**
  - g. **A summary of growth promotion studies**

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
09/26/2013

**From:** [Borders-Hemphill, Vicky](#)  
**To:** [Walker, Diana](#)  
**Cc:** [Wilkins Parker, Jamie](#)  
**Subject:** RE: Evzio naloxone autoinjector voice prompt script  
**Date:** Monday, September 16, 2013 9:43:02 AM

---

**Hi Diana,**

**Here is our response:**

**DMEPA reviewed the voice instruction prompt script for the Naloxone Auto Injector trainer and delivery devices submitted by Intelliject, Inc. on July 19, 2013, to NDA 205787. We find them to be acceptable.**

**Thanks,**

Vicky Borders-Hemphill, PharmD  
CDR, USPHS Commissioned Corps  
Safety Evaluator  
Division of Medication Error Prevention and Analysis  
FDA/CDER/OSE/OMEPRM  
Blqg 22, Room #4424  
Phone: 301-796-2225  
Email: [Vicky.Borders-Hemphill@fda.hhs.gov](mailto:Vicky.Borders-Hemphill@fda.hhs.gov)

---

**From:** Walker, Diana  
**Sent:** Monday, September 16, 2013 9:15 AM  
**To:** Borders-Hemphill, Vicky  
**Cc:** Wilkins Parker, Jamie  
**Subject:** RE: Evzio naloxone autoinjector voice prompt script

No, they haven't sent me anything. I could ask this week.

Thanks, Diana

---

**From:** Borders-Hemphill, Vicky  
**Sent:** Friday, September 13, 2013 3:27 PM  
**To:** Walker, Diana  
**Cc:** Wilkins Parker, Jamie  
**Subject:** Evzio naloxone autoinjector voice prompt script

**Hi Diane,**

**We were wondering if you received feedback from CDRH for the**

**voice script?**

**Thanks,**

Vicky Borders-Hemphill, PharmD  
CDR, USPHS Commissioned Corps  
Safety Evaluator  
Division of Medication Error Prevention and Analysis  
FDA/CDER/OSE/OMEPRM  
Bldg 22, Room #4424  
Phone: 301-796-2225  
Email: [Vicky.Borders-Hemphill@fda.hhs.gov](mailto:Vicky.Borders-Hemphill@fda.hhs.gov)

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DIANA L WALKER  
09/18/2013

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn](#)  
**Cc:** [Glen Kelley](#); [Brian Riggs](#)  
**Subject:** NDA 205787 CMC Information Request 16sep13  
**Date:** Monday, September 16, 2013 2:35:53 PM

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Dear Mr. Gunn,

I have received an information request from our CMC review team. Please update your NDA 205787 with the requested information.

**Provide all of the sections of 3.2.S, either by referencing the DMF, or by including data . Specifically, include the drug substance (DS) manufacturers together with their full addresses, DS specifications, in-house validated analytical methods used for testing of clinical batches, and batch analysis of clinical batches used in the drug product.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: [Diana.Walker@fda.hhs.gov](mailto:Diana.Walker@fda.hhs.gov)

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/s/  
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DIANA L WALKER  
09/16/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 205787

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Intelliject, Inc.  
111 Virginia Street, Suite 405  
Richmond, VA 23219

ATTENTION: Ronald D. Gunn  
Vice President, Drug Development & Regulatory Affairs

Dear Mr. Gunn:

Please refer to your New Drug Application (NDA) dated July 18, 2013, received July 19, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Naloxone Hydrochloride Injection, USP, 0.4mg per Autoinjector.

We also refer to your July 18, 2013, correspondence, received July 19, 2013, requesting review of your proposed proprietary name, Evzio. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Evzio, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If **any** of the proposed product characteristics as stated in your July 18, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dr. Diana Walker, at (301)-796-4029.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VAISHALI JARRAL  
09/13/2013

CAROL A HOLQUIST  
09/13/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

PIND 112292

MEETING MINUTES

Intelliject, Inc.  
111 Virginia Street, Suite 405  
Richmond, VA 23219

Attention: Ronald D. Gunn  
V.P., Drug Development and Regulatory Affairs

Dear Mr. Gunn:

Please refer to your Pre-Investigational New Drug Application (PIND) file for naloxone autoinjector.

We also refer to the meeting between representatives of your firm and the FDA on August 16, 2011. The purpose of the meeting was to discuss your development program for naloxone autoinjector.

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

If you have any questions, call me at (301) 796-2205.

Sincerely,

*{See appended electronic signature page}*

Kathleen Davies, M.S.  
Senior Regulatory Health Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** August 16, 2011

**TIME:** 1:30 – 2:30 PM (EST)

**LOCATION:** Food and Drug Administration  
WO Bldg 22, Room 1313  
10993 New Hampshire Ave  
Silver Spring, MD 20993

**APPLICATION:** PIND 112292

**PRODUCT:** naloxone autoinjector

**INDICATION:** complete or partial reversal of opioid depression

**SPONSOR:** Intelliject, Inc.

**TYPE OF MEETING:** type B

**MEETING CHAIR:** Sharon Hertz, M.D., Deputy Division Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**MEETING RECORDER:** Kathleen Davies, M.S., Senior Regulatory Health Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Bob A. Rappaport, M.D.	Director, DAAAP
Sharon Hertz, M.D.	Deputy Director, DAAAP
Luke Yip, M.D.	Clinical Reviewer, DAAAP
Yun Xu, Ph.D.	Acting Clinical Pharmacology Team Leader, Office of Clinical Pharmacology
Wei Qiu, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Dan Mellon, Ph.D.	Pharmacology Toxicology Supervisor, DAAAP
Danae Christodoulou, Ph.D.	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Jackie Ryan, M.D.	Office of Device Evaluation, Center for Devices & Radiological Health
Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader, ONDQA
Yelena Maslov, Pharm.D.	Office of Surveillance and Epidemiology
Zachary Oleszczuk, Pharm.D.	Office of Surveillance and Epidemiology
Kathleen Davies, M.S.	Senior Regulatory Health Project Manager, DAAAP

Intelliject, Inc.	Title
Eric Edwards	Chief Scientific Officer
Evan Edwards	VP Product Development
Ronald Gunn	VP Regulatory Affairs and Drug Development
T. Spencer Williamson IV	Chief Executive Officer
(b) (4)	Consultant, (b) (4) LLC
(b) (4)	Consultant, (b) (4) LLC

## 1.0 BACKGROUND

The Sponsor submitted a Pre-IND meeting request to discuss their development program for naloxone auto-injector (NAI). The Sponsor intends to pursue an indication for treatment of opioid depression through a 505(b)(2) regulatory pathway.

Each of the Sponsor's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the firm on August 11, 2011.

## 2. DISCUSSION

### 2.1. REGULATORY

*Question 1. Does the Agency agree that NAI will be regulated as a drug/device combination product and will be reviewed by the Division of Anesthesia and Analgesia Products?*

**FDA Response:**

**Yes. Your submission will be reviewed by this Division, with consultation from CDRH as appropriate.**

Discussion:

There was no further discussion on this point.

*Question 2. Does the Agency agree that the appropriate regulatory pathway for approval of NAI is a New Drug Application under 505(b)(2)?*

**FDA Response:**

**We agree that the 505(b)(2) regulatory pathway may be an appropriate approach for submission of an NDA for your product. However, the listed drug relied upon for approval must be a product approved under section 505(b) (NDA) of the Food, Drug, and Cosmetic Act, where a finding of safety and effectiveness has been made (see 21 CFR 314.54(a)(1)(iii). A 505(b)(2) application may not rely upon a product approved under section 505(j) (ANDA), where a finding of sameness was made. Further, you must reference and provide patent certification for that NDA product. When the NDA product drug has been discontinued and an ANDA product is listed**

in the Orange Book as the RLD for generic bioequivalence studies, the reference drug relied upon for approval of the (b)(2) is still the NDA drug, not the ANDA drug. In such a case, it is a scientific call as to what product should be used for the bridging/biolinking study(ies).

We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry *Applications Covered by Section 505(b)(2)*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dockets/04p0231/04p-0231-c000001-Exhibit-29-vol4.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You must establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

When an ANDA product must be used for a bio-bridging study, it is helpful to identify that product in your cover letter (it is not necessary to do a patent certification against an ANDA) but you must identify the NDA product as the listed drug and do a patent certification against that NDA product.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Discussion:

There was no further discussion on this point.

*Question 3. Does the Division concur that the proposed indication is appropriate for NAI?*

**FDA Response:**  
**Your proposed indication appears acceptable.**

Discussion:  
There was no further discussion on this point.

*Question 4. Does the Agency agree with the proposed TOC for the NDA for NAI including integration of the device constituent information into Module 3?*

**FDA Response:**  
**Your proposal appears acceptable. For information on electronic regulatory submissions, refer to <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm>.**

Discussion:  
There was no further discussion on this point.

*Question 5.*

(b) (4)

**FDA Response:**  
**Your product suggests a new dosing regimen for naloxone, which triggers the Pediatric Research and Equity Act. Therefore, pediatric studies will be required to demonstrate the pharmacokinetics, safety, and efficacy in pediatric patients for the proposed indication. A pediatric plan must be submitted either prior to, or as part of your NDA submission. It must include the types of proposed pediatric studies, a timeline for those studies (first patient in, last patient in, end of study, submission of final report to the Agency), and requests for deferrals and waivers accompanied justifications.**

(b) (4)

(b) (4)

**In accordance with the requirements of Titles IV and V of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. No. 110-85, 121 Stat. 823), the Pediatric Review Committee (PeRC) must review all Pediatric Assessments, Pediatric Plans, and Waiver and Deferral requests.**

Discussion:  
There was no further discussion on this point.

## 2.2. DRUG SUBSTANCE

*Question 6a. Does the Agency agree that Intelliject can reference (through a LOA) the chemistry, manufacturing, and control information in the API active DMF (conforming to the requirements of the FDA Guideline for DMF, September 1989) to provide the drug substance information for the NAI NDA?*

**FDA Response:**

**We agree that you can reference the DMF.**

**Discussion:**

There was no further discussion on this point.

*Question 6b. Acknowledging that final specification for the drug substance will be set during NDA review; does the Agency agree that the currently proposed specifications appear generally acceptable?*

**FDA Response:**

**We agree; your proposed specifications appear reasonable for IND submission. At the time of the NDA submission, specifications must comply with ICH Q3A, Q3B, and the FDA draft guidance on structural alerts.**

**For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R2), ICHQ3B(R2)). Adequate qualification must include:**

- **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.**
- **Repeat dose toxicology of appropriate duration to support the proposed indication.**

**In module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must 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 ICHQ3A(R2) and Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

**NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the ICH qualification thresholds.**

Discussion:

There was no further discussion on this point.

### 2.3. DEVICE CONSTITUENT COMPONENT

*Question 7. Does the Agency agree that the results from the device verification and validation tests planned, included certain tests conducted with EAI, would provide sufficient information to facilitate a successful FDA review of the device constituent component portion of the marketing application for NAI?*

**FDA Response:**

**We do not agree with your proposed retraction spring/piston aging testing. While**

(b) (4)

Discussion:

The Sponsor asked whether the Division found the other verification tests included in the package acceptable. The Division stated that the verification tests, other than the retraction spring/piston aging test, appear acceptable.

*Question 8. Does the Agency agree that that the software in NAI is a “moderate” level of concern as per this Guidance?*

**FDA Response:**

**We agree that the software in NAI is a “moderate” level of concern.**

Discussion:

There was no further discussion on this point.

*Question 9. Does the Agency agree that the software verification and validation testing described in this meeting package, including testing conducted with the electronic pump system assembled to EAI, will provide FDA with sufficient information to evaluate the electronic prompt system portion of the NDA for NAI?*

**FDA Response:**

**We agree that the software verification and validation testing proposal is adequate. We also note you have provided your traceability matrix in your submission. However, the traceability control you provided does not contain traceability among the requirements, specifications, identified hazards and mitigations, and Verification and Validation testing. Revise your traceability control to indicate the traceability among requirements, specifications, identified hazards and mitigations, and Verification and Validation testing.**

**The following table is a sample format for your reference.**

Hazard	Requirements Section Number	Design Section Number	Test Case Number

Discussion:

There was no further discussion on this point.



(b) (4)

**injectors. As the NAI is being marketed for home use, this is not acceptable. Your study must include representative users, which would include caregivers, patients, autoinjector-naïve and autoinjector-experienced subjects.**

Discussion:

The Sponsor stated that the study population for Study INT0803 was selected in accordance with the *Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features*, and the purpose was to validate the operating feature, not validate the overall user interface. The Sponsor stated that an additional study, IJ-1025SE-03O, will validate the overall NAI design and user interface with a representative user population. The Division stated that this appeared to be acceptable.

#### 2.4. NAI FINAL PRODUCT AND STABILITY

*Question 11. Does the Agency agree that the planned approach regarding stability and extractable/leachable studies will provide FDA with sufficient information to successfully review the final product stability portion of the NDA for NAI?*

**FDA Response:**

**We do not agree. Provide 12 months of stability data under normal storage and six months of accelerated stability data at the time of NDA submission. Provide leachable results accordingly.**

**Note, the expiration dating**

(b) (4)

(b) (4)

Discussion:

The Sponsor requested clarification as to whether leachable results at 12 months and at product expiry were acceptable. The Division strongly recommended that the Sponsor also collect

leachable data between 0 and 12 months in order to evaluate trending in the leachable data (i.e., whether the leachables are increasing or remain constant over time). The Division stated that this analysis could be done in early batches to establish a trend and then would not need to be evaluated on a routine basis. The Sponsor stated they will take the Division's recommendations under advisement and submit leachables data in the NDA for the 6- and 12-month time points.

*Question 12. Does the Agency agree with this approach to establish the stability of the drug constituent component absent the device constituent to support, for example, possible future drug constituent component process changes and technology transfer activities?*

**FDA Response:**

**We cannot answer this question fully at this time without clarity on the intent of the proposed future changes. Your approach to compare only the drug constituent of your combination product in the primary container/closure system with and without secondary packaging appears reasonable under the proposed duration (6 months) and storage conditions (normal and accelerated). Monitor and report any deviations and trends from the proposed specifications. In addition, monitor the integrity of the electronic components during stability, and assess any tendency for corrosion that may impact performance of the device.**

**We remind you that this is a drug/device combination product, and stability data and your expiry date must be representative of the entire system.**

**Discussion:**

There was no further discussion on this point.

## **2.5. HUMAN FACTORS**

*Question 13. Does the Agency agree that the Human Factors program, including the summative design validation study planned, will support the language proposed in Section 17 of the target product profile and will be sufficient for FDA to successfully review the NDA for NAI?*

**FDA Response:**

**We agree with your plan; however, three types of human factors validation testing must be performed: device usability, instructions effectiveness, and training effectiveness.**

**If actual users will receive training, then train study participants in a comparable manner, preferably at a time in advance of the device usability test session. If actual users might not be trained, then study participants should not be trained, either.**

**If the instructions for use and other labeling (packaging, etc.) would always be available in actual use, then they should be available during the device usability test session (and test participants should be allowed, but not required, to refer to the**

labeling if and as they would in actual use); otherwise, the labeling should not be present at the session.

The effectiveness of the labeling to support safe and effective use of the device must be assessed following the device usability test session (so as not to influence the tests) or in a separate session with the same or different users. Ask test participants to read the labeling or listen to the instructions and then either use the device to perform key tasks or verbally explain how they would do so, based on their understanding of the information they read. Ask the participants targeted questions related to their understanding of key concepts, such as the conditions under which to use the device or avoid using the device, etc.

In addition, we have the following comments regarding your Human Factors protocol for adequate evaluation of the proposed language in Section 17 of the label and to stimulate actual use environment:

1. **Devices used – NAI without needle or drugs: This is appropriate.**
2. **Test participants**
  - a. **It is unclear who will be prescribed this device and why.**
  - b. **It is unclear how the 3 cohorts planned to participate in the study correspond to the major user groups of the device, and how the latter two cohorts (adults aged 16-50 and aged 51-65) would be different relative to their use of the device.**
  - c. **We generally prefer that each user group consist of at least 15 individuals.**
  - d. **It is unclear how the study inclusion and exclusion criteria match the prescription guidelines given to healthcare providers, particularly relative to English-speaking, visual, hearing, and manual abilities.**
  - e. **Include opioid users in the study to represent patients who may experience opioid overdose to assess their ability to self-administer this product by utilizing the written and voice instructions.**
  - f. **We recommend including a cohort of emergency medical technicians (i.e., ambulance personnel) and hospital practitioners to assess their ability to administer Naloxone autoinjector by following written and voice instructions.**
3. **Training**

- a. **It is unclear whether actual users would be trained prior to receiving and using the device.**
- b. **The level of training given in the validation study must be equivalent or comparable (in content, format, etc.) to the training that would actually be provided to users.**

#### **4. Methods**

- a. **It is unclear what aspect of the study will be “randomized.”**
- b. **It is unclear how many trials each test participant will complete.**

#### **5. If you would rather have written instructions included, then we recommend creating two usability cohorts: one with written instructions and one without written instructions.**

#### **6. Data Analysis**

- a. **More important than calculating proportions and statistical significance of test participant performance is analyzing in depth any use errors or task failures that occur. All use errors and task failures should be analyzed to determine the root causes, the potential negative clinical consequences to the patient or the device operator (if different), and the possibility of reducing the risks through modifications to the design of the device, the labeling, or the training.**

**Please recognize that, based on the results of your Human Factors study, the written and voice instructions may require changes.**

**We will be happy to review the protocol before implementation.**

Discussion:

There was no further discussion on this point.

## **2.6. NONCLINICAL**

*Question 14. Does the Agency agree that Intelliject, Inc. can rely on the Agency's previous findings of safety and efficacy for naloxone HCl and therefore no additional nonclinical studies and no literature summaries are required to support marketing approval of NAI?*

**FDA Response:**

**You may rely upon the Agency's previous finding of safety for an FDA-approved NDA without conducting any additional toxicology studies for naloxone drug substance. However, given the initial approval date of Narcan (1971), your NDA**

submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the public domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

Additional data may be needed to support the safety of the drug product formulation. The following additional comments pertain to your NDA submission:

We note that you intend to conduct both extractable testing and leachable assessments of the primary container closure system over 6 month stability. The NDA submission must contain complete and definitive safety information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled *Container Closure Systems for Packaging Human Drugs and Biologics*. The evaluation of extractables and leachables from the drug container closure system must include specific assessments for residual monomers, solvents, polymerizers, etc. Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents *Container Closure Systems for Packaging Human Drugs and Biologics* and *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*. Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at [http://www.pqri.org/pdfs/LE Recommendations to FDA 09-29-06.pdf](http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf).

We note that you are currently proposing a drug product specification for 2,2-bisnaloxone of NMT  $\frac{(b)}{(4)}\%$ . This exceeds the current ICHQ3B(R2) qualification threshold of NMT  $\frac{(b)}{(4)}\%$  and must be adequately justified for safety. See response to question 6b regarding the nonclinical requirements for impurity/degradant qualification.

Discussion:

There was no further discussion on this point.

## 2.7. CLINICAL

*Question 15. Does the Agency agree that no additional clinical studies are required for FDA to successfully evaluate the clinical safety and efficacy portion of the NDA for NAI?*

**FDA Response:**

**We do not agree. You will need to conduct a bioequivalence study in order to demonstrate pharmacokinetic comparability between your product and the listed drug product.**

**Be advised the Agency is considering a public scientific workshop on non-hospital use of naloxone in the treatment of opioid overdose.**

**If approved, NAI will be the first autoinjectable naloxone marketed in the United States for use in the out-of-hospital setting. Given that this represents a novel setting for naloxone use as a treatment for opioid overdose, an Advisory Committee may be convened to provide input on this new drug application.**

Discussion:

The Sponsor requested clarification as to why no biowaiver would be granted for this product. The Division explained that biowaivers cannot be granted for autoinjectors that reference a non-autoinjector product. Drug delivery is dependent on the needle size and depth of delivery and a study is necessary to demonstrate comparable exposure.

The Division noted that a relative bioavailability study would be acceptable *in lieu* of a strict bioequivalence study. The Sponsor should ensure that the study demonstrates that the autoinjector will deliver naloxone similarly to the currently approved product and should try to be as close to bioequivalent as possible. If the autoinjector is not bioequivalent to the reference product and demonstrates a higher systemic exposure than the reference product, then additional data or a justification would be required to assure that the higher exposure did not represent a safety concern. If the autoinjector demonstrates a lower systemic exposure than the reference product, then additional data or a justification would be required to support that adequate efficacy can be expected. Considering naloxone has a relatively large therapeutic index window, the concern would be greater if the autoinjector delivers less than the referenced product. The Division recommended that an adequate sample size be calculated, in order to obtain a reliable estimation of the PK parameters from the relative bioavailability study. The Division also recommended that the Sponsor use the bioequivalence method to analyze the data. The Division stated that we can provide feedback on the study design for this study.

(b) (4)

### 3.0 ACTION ITEMS

1. The Division clarified that the device verification testing is appropriate except for the retraction spring/piston aging testing.
2. The Division clarified that the design for the needle retraction usability study is appropriate.
3. The Sponsor will take under advisement that the Division would like an additional time point (6 months) between 0 and 12 months for the leachables study.
4. The Sponsor understands that no biowaiver will be granted for this product.
5. The Sponsor will submit a relative bioavailability study protocol, designed like a bioequivalence study, for review by the Division. It is recommended the Sponsor clearly state in the cover letter that they are seeking the Division's feedback on the protocol.
6.  (b) (4)

### 4.0 ATTACHMENTS AND HANDOUTS

The Sponsor's slides from the meeting are attached to the minutes.



Pre-IND# 112,292  
Naloxone Auto-Injector Meeting  
August 16<sup>th</sup>, 2011  
1:30 – 2:30 PM (EST)

Food and Drug Administration  
WO Bldg 22, Room 13113  
10992 New Hampshire Ave  
Silver Spring, MD 20993

# Meeting Objectives/Agenda

1. Demonstrate the use of NAI (5 minutes)
2. Obtain close alignment with the FDA on development requirements and expected labeling for NAI (45 minutes)
  - Question #7: Device verification testing
  - Question #10: Sharps injury prevention data requirements
  - Question #11: Leachables testing time points
  - Question #15: Clinical data requirements
  - Labeling Clarification pertaining to intended population (b) (4)
3. Conclusions/Actions (5 minutes)



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## Question #7 and FDA Response

Does the Agency agree that the results from the device verification and validation tests planned, including certain test results from tests conducted with EAI, would provide sufficient information to facilitate a successful FDA review of the device constituent component portion of the marketing application for NAI?

### FDA Response:

We do not agree with your proposed retraction spring/piston aging testing.

(b) (4)



## **Question #7 Clarification**

**Intelliject Agrees:** Retraction Spring/Piston Aging Testing of NAI will be conducted as part of the accelerated age testing program and will be included in the NDA.

**Follow-up Question:** Is the Agency in agreement with the other tests presented to support the verification of the device constituent for NAI?

## Question #10 and FDA Response

Does the FDA agree that Intelliject can rely on data from Study (b) (4) conducted with (b) (4) as NAI, along with in vitro testing of NAI, in order to validate the sharps injury prevention feature of NAI?

### FDA Response:

We do not agree that you can rely on data from Study (b) (4) to validate the sharps injury prevention feature of NAI.

(b) (4) As the NAI is being marketed for home use, this is not acceptable. Your study must include representative users, which would include caregivers, patients, autoinjector-naïve and autoinjector-experienced subjects.

i

## Question #10 Clarification

(b) (4)

- Study IJ-1025SE-030 will validate overall NAI design user interface with representative user populations in a simulated use environment
  - This is consistent with the validation program for EAI<sup>2</sup>

<sup>1</sup> Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features issued August 9, 2005.

<sup>2</sup>Intelliject's epinephrine auto-injector (EAI) received tentative approval 7/29/2011

## Question #11 and FDA Response

Does the Agency agree that the planned approach regarding stability and extractable/leachable studies will provide FDA with sufficient information to successfully review the final product stability portion of the NDA for NAI?

### FDA Response:

We do not agree. Provide 12 months of stability data under normal storage and six months of accelerated stability data at the time of NDA submission. Provide leachable results accordingly.

Note, the expiration dating

(b) (4)

(b) (4)

## Question #11 Clarification

Intelliject Agrees - 12 months of stability data under normal storage (25°C/60%RH) and six months of accelerated (40°C/75%RH) stability data will be included in the NDA at the time of NDA submission.

Follow-up Question: Does the Agency agree that leachable results at 12 months and at product expiry under normal storage (25°C/60%RH) will be sufficient to support approval of NAI?

## Question #15 and FDA Response

Does the Agency agree that no additional clinical studies are required for FDA to successfully evaluate the clinical safety and efficacy portion of the NDA for NAI?

### *FDA Response:*

*We do not agree. You will need to conduct a bioequivalence study in order to demonstrate pharmacokinetic comparability between your product and the listed drug product.*

*Be advised the Agency is considering a public scientific workshop on non-hospital use of naloxone in the treatment of opioid overdose.*

*If approved, NAI will be the first auto-injectable naloxone marketed in the United States for use in the out-of-hospital setting. Given that this represents a novel setting for naloxone use as a treatment for opioid overdose, an Advisory Committee may be convened to provide input on this new drug application.*

## Question #15 Clarification

- Unclear why NAI does not Qualify for a Waiver of In-vivo Bioavailability?
  - NAI meets 21 CFR 320.22(b)(1):
    - » Parenteral solution intended solely for administration by injection
    - » Same active & inactive ingredients at the same concentrations
  - Current naloxone product received a waiver of In-vivo bioavailability (MINI-I-JET prefilled syringe)
  - Previous combination products approved without In-vivo Bioavailability (Teva Sumatriptan prefilled syringe, TwinJect®, EpiPen®)
  - In-vivo bioavailability was not required for approval of EAI

## Question #15 Clarification (continued)

### Possible Clinical Bridging Options (BA or BE or limited confirmatory testing)<sup>1</sup>

- Bioequivalence Study
  - » Relevance in relation to therapeutic window and technical challenges
  - » Not strictly required<sup>1,2</sup>
- Bioavailability Study
  - » Document the bioavailability of NAI and Listed Drug
- Limited Pharmacodynamic Study (i.e. Confirmatory Testing as defined in 54 FR 28872 at 28880)

<sup>1</sup> October 1999 DRAFT Guidance for Industry: Applications Covered by Section 505(b)(2).

<sup>2</sup> Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (1998), Section II.C.1.d.

# Labeling Clarification

Does FDA agree that Section 1 *Indications and Usage* for NAI would include text similar to

(b) (4)



# Conclusions/Actions



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHLEEN M DAVIES  
09/01/2011

**From:** [Walker, Diana](#)  
**To:** [Ronald Gunn](#)  
**Cc:** [Glen Kelley](#)  
**Subject:** RE: IND 112292/NDA 250787 - Intelliject Naloxone Auto-Injector (NAI) - Questions for CDRH Compliance  
**Date:** Monday, August 05, 2013 10:25:50 AM  
**Importance:** High

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Dear Ron,

I have received the following responses to your questions below.

**Question #1:**

Intelliject and its supplier(s) do not typically provide copies of quality procedures in a NDA due to the burden associated with updating the NDA each time the quality procedure is updated.

- a) Will submission of quality procedures, such as those referenced in the Guidance, help facilitate the most efficient review possible by CDRH?

**Response:** Yes, it will. However, we do not request that you submit all your procedures. Key procedures and general master plans with a sampling of procedures are normally adequate.

- b) If so, does FDA agree that Intelliject and its supplier(s) do not have to update the NAI NDA if/when these quality procedures are updated post-approval?

**Response:** Yes, FDA agrees that the NAI NDA will not need to be updated when these quality procedures are updated. Normally, post-market changes in quality procedures are evaluated during routine post-market inspections.

**Question #2:**

Based on the activities each supplier performs, Intelliject plans to submit quality system information for (b) (4) and Intelliject only. (b) (4), because it performs final assembly and device performance release testing, and Intelliject, because we maintain the Design History File and conduct final release of NAI. We do not plan to submit quality system information for (b) (4) because none of these suppliers is involved in the device design, final device assembly or final device testing.

Does FDA agree with Intelliject's plan to only submit quality system information, as referenced in the Guidance, for (b) (4) and Intelliject?

**Response:** Yes, FDA agrees that quality system information is only required for (b) (4) and Intelliject and should be representative of the activities conducted at each facility.

**Question #3:**

In the pre-NDA meeting minutes dated June 26, 2013, Question #5, FDA and Intelliject agreed to the location and eCTD leaf titles for documents related to the Device Constituent Component of NAI. Intelliject proposes that any Quality System information be placed in 3.2.P.7 with the addition of an eCTD leaf title of "Auto-Injector QS – XXX" where XXX identifies the manufacturer (e.g., (b) (4) Intelliject, etc.).

Does FDA agree with the proposed location and eCTD leaf titles for Quality System information

in the NAI NDA?

**Response:** The FDA agrees that section 3.2.P.7 with the addition of an eCTD leaf title of “Auto-Injector QS – XXX” where XXX identifies the manufacturer (e.g., (b) (4), Intelliject, etc.) is the correct place to locate quality system information.

Regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
Fax: 301-796-9723/9713  
Email: Diana.Walker@fda.hhs.gov

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**From:** Ronald Gunn [mailto:ronald.gunn@intelliject.com]  
**Sent:** Thursday, August 01, 2013 10:55 AM  
**To:** Walker, Diana  
**Cc:** Glen Kelley  
**Subject:** IND 112292/NDA 250787 - Intelliject Naloxone Auto-Injector (NAI) - Questions for CDRH Compliance

Dear Diana,

I am writing to communicate the specific Quality System information that Intelliject plans to include in our NDA for our Naloxone Auto-Injector (NAI) and confirm that this level of quality system information will facilitate the most efficient review possible by CDRH.

Background

Per FDA’s pre-NDA meeting minutes (June 26, 2013), CDRH indicated that the type and scope of documents that may be provided to support the NDA are defined in the “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff: issued on February 3, 2003 (hereinafter “Guidance”). Section 1 of the Guidance states “When multiple facilities are involved in the design, assembly, or processing of the device, you should submit applicable QS information for each facility in separate volumes that clearly identify the facility to which it applies.”

The following primary suppliers are involved in the manufacture of NAI:

- 
- 

(b) (4)

- 
- 
- 
- 

Question #1:

Intelliject and its supplier(s) do not typically provide copies of quality procedures in a NDA due to the burden associated with updating the NDA each time the quality procedure is updated.

- a) Will submission of quality procedures, such as those referenced in the Guidance, help facilitate the most efficient review possible by CDRH?**  
**b) If so, does FDA agree that Intelliject and its supplier(s) do not have to update the NAI NDA if/when these quality procedures are updated post-approval?**

Question #2:

Based on the activities each supplier performs, Intelliject plans to submit quality system information for (b) (4) and Intelliject only. (b) (4), because it performs final assembly and device performance release testing, and Intelliject, because we maintain the Design History File and conduct final release of NAI. We do not plan to submit quality system information for (b) (4) because none of these suppliers is involved in the device design, final device assembly or final device testing.

**Does FDA agree with Intelliject's plan to only submit quality system information, as referenced in the Guidance, for (b) (4) and Intelliject?**

Question #3:

In the pre-NDA meeting minutes dated June 26, 2013, Question #5, FDA and Intelliject agreed to the location and eCTD leaf titles for documents related to the Device Constituent Component of NAI. Intelliject proposes that any Quality System information be placed in 3.2.P.7 with the addition of an eCTD leaf title of "Auto-Injector QS – XXX" where XXX identifies the manufacturer (e.g., (b) (4) Intelliject, etc.).

**Does FDA agree with the proposed location and eCTD leaf titles for Quality System information in the NAI NDA?**

Should you have any questions or require additional information, please do not hesitate to contact me at (804) 640-9447.

With sincere regards,

Ron

Ronald D. Gunn  
Vice President, Drug Development & Regulatory Affairs

Intelliject  
111 Virginia Street, Suite 405  
Richmond, VA 23219

(Office) 804.545.6376  
(Mobile) [REDACTED] (b) (6)  
(Fax) 804.545.6219

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANA L WALKER  
08/05/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

IND 112292

MEETING MINUTES

Intelliject, Inc.  
111 Virginia Street, Suite 405  
Richmond, VA 23219

Attention: Ronald D. Gunn  
V.P., Drug Development and Regulatory Affairs

Dear Mr. Gunn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for naloxone autoinjector (NAI).

We also refer to the meeting between representatives of your firm and the FDA on June 4, 2013. The purpose of the meeting was to discuss the status of development activities to date and Intelliject's plans for submission of an NDA for NAI (naloxone hydrochloride auto-injector).

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

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

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

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

**Meeting Date and Time:** June 4, 2013, 3:00 p.m. (Eastern)  
**Meeting Location:** 10903 New Hampshire Avenue  
 White Oak Building 22, Conference Room: 1315  
 Silver Spring, Maryland 20903

**Application Number:** IND 112292  
**Product Name:** Naloxone autoinjector (NAI)  
**Indication:** (b) (4)  
**Sponsor/Applicant Name:** Intelliject, Inc.

**Meeting Chair:** Joshua Lloyd, M.D., Clinical Team Leader, DAAAP  
**Meeting Recorder:** Diana Walker, Ph.D., Sr. Regulatory Project Manager, DAAAP

<b>Industry Representatives</b>	<b>Title</b>
Frank Blondino	Director Drug Development
Eric Edwards	Chief Medical Officer
Ronald Gunn	V.P. Drug Development and Regulatory Affairs
Neil Hughes	Chief Commercial Office
Glen Kelley	Director Regulatory Affairs
Spencer Williamson	Chief Executive Officer
Ned Ruffin	General Counsel
<b>FDA</b>	<b>Title</b>
Bob A. Rappaport, M.D.	Division Director, DAAAP
Sharon Hertz, M.D.	Deputy Director, DAAAP
Joshua Lloyd, M.D.	Clinical Team Leader, DAAAP
Neville Gibbs, M.D.	Medical Officer, DAAAP
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader
Steven Hertz	Quality Reviewer, OMPQ/OC
Jessica Cole, Ph.D.	Microbiology Reviewer, OPS/NDMS
Daniel Mellon, Ph.D.	Pharmacology-Toxicology Supervisor, DAAAP
Carlic Huynh, Ph.D.	Nonclinical Reviewer, DAAAP
Prasad Peri, Ph.D.	Branch Chief, ONDQA
Julia Pinto, Ph.D.	Chemistry, Manufacturing, and Controls (CMC) Team Lead, ONDQA
Arthur Shaw, Ph.D.	CMC Reviewer, ONDQA
M. Isabel Tejero, M.D., Ph.D.	CDRH Compliance
Quynh Nhu Nguyen	Human Factors, CDRH
Vicky Borders-Hemphill	Reviewer, DMEPA
Jamie Wilkins-Parker	Team Leader, DMEPA

Carol Holquist	Director, DMEPA
Patricia Love, M.D., M.B.A.	Deputy Director, Office of Combination Products
Reema Mehta, Pharm.D., M.P.H.	Team Leader, DRISK
Juandria Williams, Ph.D.	Quality Reviewer, OMPQ/OC
Hari Cheryl Sachs, M.D.	Team Leader, Pediatrics, Pediatric and Maternal Health Staff, OND, IO
Erica L Wynn, M.D., M.P.H.	Medical Officer, Pediatrics, PMHS
Diana Walker, Ph.D.	Sr. Regulatory Project Manager, DAAAP

## 1.0 BACKGROUND

The purpose of this meeting is to review the status of the development program for NAI and obtain agreement on the content and timing of the NDA for NAI. NAI is a drug-device combination product consisting of a single-use auto injector that delivers 0.4 mg naloxone hydrochloride (HCl) via subcutaneous or intramuscular injection.

The Preliminary Meeting Comments were sent to the Sponsor via email on May 31, 2013. The Sponsor submitted a document via email on June 3, 2013, which contained slides that they planned to present at the meeting, and specific Agency responses that they would like to clarify during the face-to-face meeting. The slides are attached to these minutes.

The Sponsor's original questions are incorporated below in *italics* followed by the FDA preliminary responses in **bold** font. Discussions that took place during the meeting are captured following the question to which it pertains in normal text.

## 2.0 DISCUSSION

*Question 1. Does the FDA agree to review the NAI NDA as a rolling submission?*

### **Agency Response:**

**We agree that your proposed product, NAI, which has been granted a Fast Track designation for the (b) (4) can be reviewed as a rolling NDA submission.**

### Discussion

There was no additional discussion of this question.

*Question 2. Does the FDA agree with the content, format and timing of submissions in the proposed rolling submission for the NAI NDA?*

### **Agency Response:**

**We generally agree, however, we have the following comments regarding the content and format of your proposed rolling submission for the NAI NDA:**

1. We note that you intend to submit the request for proprietary name review to your IND. You must also submit this request to the NDA.
2. If you intend to submit all of your administrative documents in Submission #1, any documents (e.g., patent certification, debarment statement, etc.) for which changes have occurred in the interim must be updated in the final submission.
3. We remind you, as discussed at the pre-IND meeting, that your NDA submission must contain information on potential leachables and extractables from the drug container closure system, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device must include specific assessments for residual monomers, solvents, polymerizers, and any other relevant compounds. Based on identified leachables, you must provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, refer to *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation*  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf>

and

*Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf>

For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity must not exceed (b) (4) mcg/day total daily exposure or must be adequately qualified for safety. Provide a toxicological risk assessment for any non-genotoxic leachable that exceeds (b) (4) mcg/day.

4. CDRH Office of Compliance document request

**This request for information is based on the statement in the meeting briefing package that the final assembly of the combination product will follow 21 CFR part 820 (section 2.6 of IJ-1200MFG-03O Validation Master Plan NAI Auto-Injector).**

**For guidance regarding the type and scope of documents that may be provided to support compliance with applicable device manufacturing regulations, refer to the document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>**

Discussion

There was no additional discussion of this question.

*Question 3. Does the FDA agree that the information planned for inclusion in Submission #1 is sufficient for the FDA to complete its review of the proposed labeling (including voice prompts) for NAI?*

**Agency Response:**

**Based on the proposed submission timeline, we can begin reviewing labeling with Submission #1 and provide feedback as soon as feasible. However, we cannot complete the review of the proposed labeling until all of the relevant data has been submitted (e.g., the clinical study report and datasets for Clinical Bioavailability Study IJ-900DV-03O).**

Discussion

The Sponsor sent the following information and question to the Agency after receipt of the responses and in advance of the meeting. “The lead-time for obtaining electronic chips containing the approved voice prompt script is (b) (4) Intelliject is working with (b) (4) suppliers to shorten this lead time (b) (4) Does FDA agree to provide feedback on the voice prompt script separately as a first priority and prior to submission of the clinical bioavailability study report and datasets?”

The Division of Medication Errors and Prevention Analysis (DMEPA) agreed that, in combination with CDRH and the clinical review team, the review of the voice prompt will begin upon submission, and comments will be provided to the Sponsor as soon as possible. The Sponsor clarified that the formative testing results on the voice prompt and entire Human Factors study report will be included in the first submission. The Sponsor also informed the Agency that the voice prompt script is the same as the Auvi-Q script. DMEPA reiterated to the Sponsor that, as in the previous analysis with Auvi-Q, the script and voice prompt will be evaluated in the clinical context for which the proposed product is intended.

*Question 4. Does the FDA agree that the NAI NDA will be sufficiently complete to permit a substantive review (i.e., sufficient for FDA to file the NDA for review and initiate*

*the PDUFA review clock) once Submission #1 and Submission #2 have been submitted (i.e., before Submission #3)?*

**Agency Response:**

**No, we do not agree. We will make an effort to perform a substantive review of complete sections of the application as soon as possible. However, for a rolling review, the review clock does not start until after the last submission is submitted and you have informed the Agency that the NDA is complete. Following notification that the application is complete, the Agency will make a filing determination within the usual time frame (See 21CFR 314.101).**

Discussion

There was no additional discussion of this question.

*Question 5. Does FDA agree with the proposed location of the Device Constituent Component information in Section 3.2.P.7 and the addition of the "Auto- Injector" prefix to the eCTD leaf titles for documents containing this information?*

**Agency Response:**

**Yes, we agree. Additionally, the documents requested by the CDRH Office of Compliance can be located in this module (refer to our response to Question #2).**

Discussion

There was no additional discussion of this question.

*Question 6. Does the FDA agree that there can be no 30-Month Stay of the NAI NDA if no patents claiming the drug, drug product or method of use for the Reference Listed Drug are submitted to FDA's Orange Book Database prior to the first submission (i.e., Submission #1) of the NAI NDA rolling submission?*

**Agency Response:**

**No, we do not agree. We note that a 30-month stay of a 505(b)(2) application will only ensue if a patent covering the reference listed drug is submitted to FDA's Orange Book Database before the date the 505(b)(2) application is submitted to the FDA. The application is considered submitted only after the final submission of the rolling NDA has been submitted and you have informed the Agency that the NDA is complete.**

Discussion

The Sponsor sent the following information and question to the Agency after receipt of the responses and in advance of the meeting. "Does FDA agree that the word "date" in "before the date the 505(b)(2) application is submitted" is the date of the final submission of the rolling NDA (along with a letter stating the NDA is complete) and not the date that the final submission is "accepted for filing" by FDA?"

The Agency clarified that the word “date” means the date on which the final submission of the rolling NDA is received and not the filing date. If an application is not accepted for filing, the date would be updated upon receipt of the resubmission.

*Question 7. Does the FDA agree with the proposed text in the Indication section and location of updated exemplary opioids in the Dosage and Administration section of the Prescribing Information for NAI as shown in the Target Product Profile in Appendix 10?*

**Agency Response:**

**We will consider the proposed labeling changes during the NDA review. Provide additional support for the proposed changes to the indication statement (i.e., addition of the text (b) (4) and explain how you plan to define this population.**

Discussion

The Sponsor sent the following information and question to the Agency after receipt of the responses and in advance of the meeting (see Attachment 2: Meeting Slides, for the information presented in the meeting). The Sponsor reviewed the information provided on slides 10 – 14 of the meeting handout and asked

*“Does FDA agree that the types of supporting information as presented in the meeting (i.e., market research and published data) would be sufficient for FDA to complete a review of the proposed changes in the indication statement (i.e., addition of (b) (4) (b) (4)”*

The Division asked the Sponsor to clarify the types of published data they plan to submit in support of the proposed indication statement. The Sponsor clarified that they intend to submit literature studies describing fatal overdoses, and referred to the information on Slide #13 of the pre-NDA meeting handout (supplied by the Sponsor, see Attachment 2). The Sponsor stated that there is a lot of literature describing people (b) (4)

(b) (4)

The Agency is currently reviewing the (b) (4) literature to determine its strengths and weaknesses and is evaluating whether the conclusions in the literature are supported by the data. While the Division agreed that literature-based support may be helpful, it would also be helpful to obtain information from commercial databases that capture information on opioid overdoses and provide descriptive information on those patients who overdosed, including the source of the drug involved in the overdose.

The Division recommended that the Sponsor propose labeling that includes a population that is as broad as possible, (b) (4)

(b) (4)

Sponsor agreed to submit the supportive information, market research, and publicly available literature in support of their indication statement. The Sponsor also presented information related to physician perception of (b) (4) and asked the Division whether research on physician perception would be useful. The Division noted that reports of physician perception are anecdotal and not as useful as information collected from commercially-available databases (e.g., poison control centers) that capture the population who has overdosed on opioids

(b) (4)

The Division acknowledged that it will be important to distinguish NAI from the reference product in regard to the indication statement, but that this will be a “real-time” process that is carried out during the course of the NDA review to determine the most appropriate language.

(b) (4)

Question 8.

(b) (4)

**Agency Response:**

**No we do not agree. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. An NDA application for naloxone auto-injector (NAI) will be subject to PREA because it proposes both a new dosing regimen and a new indication.**

**Your proposed product will be used as a fixed dose regimen**

(b) (4)

**Specifically you propose that**

(b) (4)

**(b) (4) In contrast, the current labeling for Naloxone hydrochloride provides**

(b) (4)

(b) (4)

(b) (4)

**dosing regimen. Therefore, your product triggers the requirements under PREA because your proposed dosing is considered a new dosing regimen.**

**We also note that you propose to include**

(b) (4)

**(b) (4) in the indication statement. This represents a change in the indication for naloxone and would also serve to trigger the requirements under PREA (also refer to our response to Question #7 regarding the proposed changes to the indication statement).**

Discussion

There was no additional discussion of this question, however, the Pediatric and Maternal Health Staff is providing the following clarification as a post-meeting note.

**Post-meeting Note:** To clarify our response to Question 8, we are adding the following underlined words to this sentence from our response above: “Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable at the time of approval.”

Question 9. *If FDA does believe that NAI represents a new dosing regimen of naloxone, does the FDA agree* (b) (4)

(b) (4)

**Agency Response:**

(b) (4)

Under the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA now requires sponsors to submit a pediatric study plan (PSP) within 60 days of an End-of-Phase 2 meeting held on or after November 6, 2012. If your application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA). If your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm> . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).

A request for waiver of studies in any pediatric age groups may be made as part of a PSP or pediatric plan. If you believe that a waiver for any pediatric age groups would be

appropriate, at the time of NDA submission submit any clinical, epidemiological and use data (including database information from poison control centers) to support your waiver requests. A waiver for one or more of the pediatric age groups may be granted for one of the following reasons:

- Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).
- The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients in the pediatric age group(s) for which a waiver is being requested.
- The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(b) (4)

(b) (4)

Discussion

There was no additional discussion of this question.

*Question 10. Does FDA agree that NAI will not require a REMS?*

**Agency Response:**

**At this time, we do not have sufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.**

Discussion

There was no additional discussion of this question.

*Question 11. Does FDA believe that it is possible a future opioid REMS may require the co-prescription of a naloxone product? And if so what is the likelihood and probable timeframe?*

**Agency Response:**

**We do not have any information regarding the possibility of a future opioid REMS that requires the co-prescription of a naloxone product.**

Discussion

There was no additional discussion of this question.

*Question 12. Provided the final results confirm the draft results presented, does the FDA agree that an Advisory Committee will not be necessary for the review of the NAI NDA?*

**Agency Response:**

**The decision about the need to convene an Advisory Committee will be made at the time of NDA submission and will be based on the results of the review of the content of the NDA package. However, based on the information currently available, it is unlikely that an Advisory Committee will be necessary.**

Discussion

There was no additional discussion of this question.

*Question 13. What is the earliest date that FDA believes a NAI NDA PAI could be scheduled at (b) (4)?*

**Agency Response:**

**It is the Agency's expectation that all of the facilities submitted in an application are ready for inspection at the official date of submission. On-site inspections in support of filed applications may occur at any time. It is your responsibility to ensure that the facilities are ready for inspection at the time of the NDA submission. A facility that is found not ready for inspection may be considered unacceptable regarding compliance to CGMP. Such a finding may delay approval of your application (FD & C Act 505(d)(3)). Please refer to Section 3.0 "Manufacturing Facilities" for more information.**

Discussion

There was no additional discussion of this question.

*Question 14. Does Intelliject's justification for the proposed use of (b) (4) sufficiently address FDA's Comment 2a from the December 13, 2012, letter? (b) (4)*

**Agency Response:**

**Yes, (b) (4) following information about the (b) (4) (b) (4) simulations (b) (4) Include the (b) (4) (b) (4) container/closure used, line speed, fill volume, holding period (if any), number of units filled, number of units rejected (with a brief reason), number of units incubated, and the number of positive units. Refer to the**

following Guidance document(s) when preparing your NDA submission:

(b) (4)

Discussion

There was no additional discussion of this question.

*Question 15. Does Intelliject's response to establish limits and include the bioburden test as an (b) (4) sufficiently address FDA's Comment 2b from the December 12, 2012, letter?*

**Agency Response:**

**We agree with the inclusion of a (b) (4) bioburden test and agree with inclusion of the test method and specification in the NDA. We do not agree with your proposed bioburden limit, which you state will be based on the (b) (4). The control of bioburden has two functions; to insure the bioburden load is below the (b) (4) and to prevent the adulteration of the drug product with microbial by-products. The bioburden limit must reflect the routine microbiological control of the (b) (4) product. The registration batches had a bioburden of (b) (4) CFU/mL. Set the bioburden limit in accordance with the process capability.**

Discussion

There was no additional discussion of this question.

*Question 16. Does the FDA agree that water filled cartridges are appropriate as surrogates for routine (b) (4) sterilization load and lot testing?*

**Agency Response:**

**Yes, water-filled cartridges may be used as a surrogate.**

Discussion

There was no additional discussion of this question.

*Question 17. Does the FDA agree that the description above is sufficient for FDA to understand how sterility of the drug flow path (i.e., Needle) and the space around the Needle are maintained?*

**Agency Response:**

**The explanation provided appears reasonable. The sterilization validation information will be reviewed after submission of the NDA.**

Discussion

There was no additional discussion of this question.

*Question 18. Does FDA agree that the biocompatibility reports from studies conducted with the Auvi-Q (NDA 201739 (needle (b) (4) (b) (4) will be sufficient to support the biocompatibility of the Needle in NAI?*

**Agency Response:**

**If the needle that you intend to use with the NAI is the same needle and manufacturer as in the NDA for Auvi-Q, then FDA will accept the biocompatibility testing previously submitted. However, if the needle for the NAI is of the same material specification but not of the same manufacturer, you must submit independent biocompatibility testing results for your NAI needle as per ISO 10993.**

Discussion

There was no additional discussion of this question.

*Question 19. Provided that the data from these studies validate the user interface for NAI, does the FDA agree that no further device usability, instruction effectiveness, or training effectiveness studies will be required to support approval of the NAI NDA?*

**Agency Response:**

**Provided that the data from the summative Human Factors/usability validation study demonstrate that the device and its associated labeling and training are safe and effective for its intended use, users, and use environment, we do not believe that you will be required to conduct additional Human Factors/usability studies. However, we may have additional comments after we have an opportunity to review the Human Factors/usability test report.**

Discussion

There was no additional discussion of this question.

*Question 20. Provided that the data from these studies remain within product specifications, does the FDA agree that the data will support a (b) (4) month shelf life for NAI at the time of NAI NDA Submission #3?*

**Agency Response:**

**No, we do not agree. Only 12 months of stability data from the registration lots will be available at the time of NAI NDA Submission #3. We expect at least (n-12) months of stability data to be available for review at the time of NDA submission, where n = proposed shelf life.**

Discussion

The Sponsor sent the following questions to the Agency after receipt of the responses and in advance of the meeting (in *italicized* font).

*“Does the FDA agree that provided 12 months of real-time stability data are available for review at the final NDA submission and the results remain within product specifications then the proposed shelf-life could be 24 months (i.e., 24-12=12)?”*

The Agency agreed that, if 12 months of stability data are provided at the time of NDA submission, the Sponsor could potentially receive 24 months shelf-life, provided that there is compliance with ICH Q1E guidelines and that there is no trend in the data to the contrary.

(b) (4)

The Agency agreed that this proposal was reasonable and that either a submission of the information in a CBE-0 or in the Annual Report is acceptable.

*Question 21. Provided the final results confirm the draft results presented, does the FDA agree that the draft results from comparative bioavailability study IJ-900DV-030 provide a clinical bridge to the established efficacy and safety of the Reference Listed Drug and that no further clinical studies are necessary?*

**Agency Response:**

**We agree that, if the draft results of the comparative bioavailability study, IJ-900DV-030, are confirmed upon final review, no further clinical studies are necessary.**

Discussion

There was no additional discussion of this question.

### 3.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

In addition please be sure you have indicated what sites are involved in the manufacture of critical component finished combination product and consumables and follow recommendations in the Final Rule Combination Product Good Manufacturing Practice; <http://www.fda.gov/downloads/CombinationProducts/UCM336194.pdf>.

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**4.0 ACTION ITEMS**

- 4.1 The Agency agreed that the review of the voice prompt will begin upon submission, and comments will be provided to the Sponsor as soon as possible.
- 4.2 The Sponsor agreed to submit supportive information, market research, and publicly available literature to appropriately define the patient population in order to write an accurate indication section in the product label. The Division recommended that the Sponsor provide as much information as possible from databases looking at actual events and the Sponsor agreed.

- 4.3 The Agency agreed that if, 12 months of stability data are provided, the Sponsor could potentially receive 24 months shelf-life, provided that there is compliance with ICH and that there is no trend to the contrary.
- 4.4 The Agency agreed that the shelf-life of NAI can be extended through post-approval submission of real-time stability data in CBE-0 supplements.

## **5.0 ATTACHMENTS AND HANDOUTS**

- 5.1 Attachment 1: Additional Comments for Pre-NDA Stage of Drug Development
- 5.2 Pre-NDA Meeting Handouts supplied by Intelliject, Inc.

**Attachment 1:**  
**Additional Comments for Pre-NDA Stage of Drug Development**

**Regulatory Comments**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the

proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

**Nonclinical Comments**

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

2. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.
3. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

As noted in the document cited above, "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).

4. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- 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. Repeat dose toxicology of appropriate duration to support the proposed indication.
5. Genotoxic or carcinogenic impurities that contain a structural alert for genotoxicity must be either reduced to NMT <sup>(b) (4)</sup> mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT <sup>(b) (4)</sup> mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

6. 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 ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.
7. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. Certain drug products are considered to present a high concern for risk, for example, liquid formulations or drugs in patches or other devices employed for parenteral delivery. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables you will need to provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents “Container Closure Systems for Packaging Human Drugs and Biologics” and “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation.” For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed (b) (4) mcg/day total daily exposure or be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds (b) (4) mcg/day.
8. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

#### **Chemistry, Manufacturing and Control (CMC) Comments**

1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
2. Include at least 12 months of long-term data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the

proposed expiry dating.

3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.
4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

**The Abuse Potential section of the NDA is submitted in the eCTD as follows:**

*Module 1: Administrative Information and Prescribing Information*

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (nonclinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

*Module 2: Summaries*

2.4 Nonclinical Overview

This section should include a brief statement outlining the nonclinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

*Module 3: Quality*

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

#### *Module 4: Nonclinical Study Reports*

##### 4.2.1 Pharmacology

###### 4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

###### 4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

#### *Module 5: Clinical Study Reports*

##### 5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

###### 5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

### **General Clinical Comments**

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

### **Sites for Inspection**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested, as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

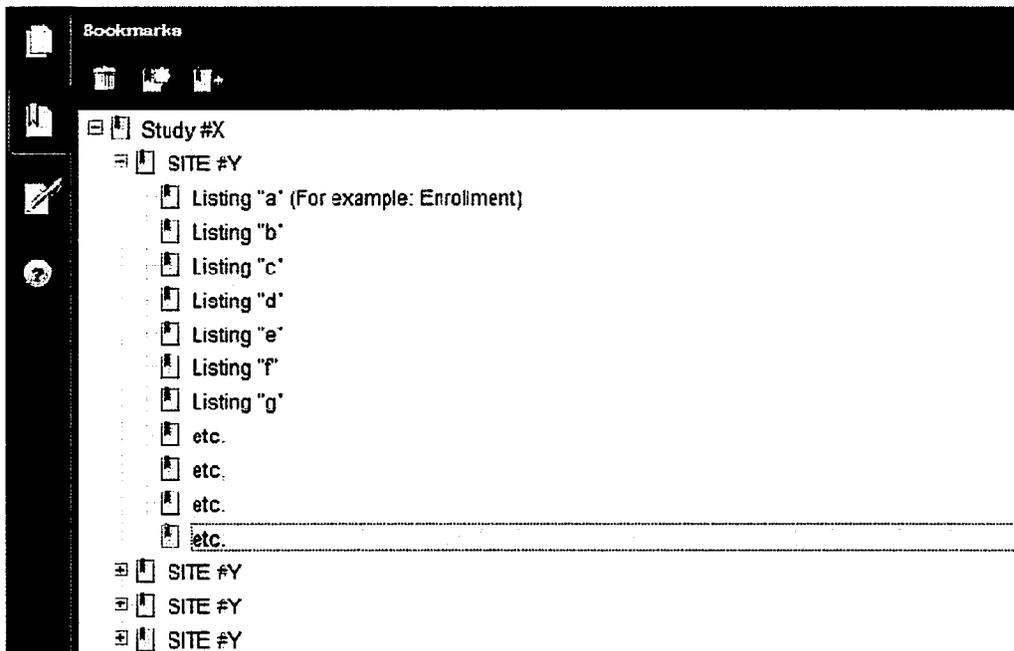
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Subpart 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

- I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**
1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
    - a. Site number
    - b. Principal investigator
    - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
    - a. Number of subjects screened for each site by site
    - b. Number of subjects randomized for each site by site, if appropriate
    - c. Number of subjects treated who prematurely discontinued for each site by site
  3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
    - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
    - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
    - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies

- d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 3 study using the following format:



### III. Request for Site Level Dataset

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Subpart 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## Subpart 1

### 1. Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

#### 1.1. Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### 1.2. Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

##### *Site-Specific Efficacy Results*

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

**Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)**

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "-1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug X), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events)	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860), if unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860), if unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

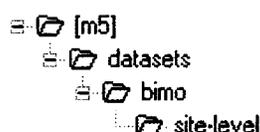
INITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

**Subpart 2**  
**Technical Instructions:**  
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

## Pediatric Plan

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

## Common PLR Labeling Errors

### Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRul es/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

**Contents (Table of Contents):**

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
20. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information (FPI):**

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
24. Do not refer to adverse reactions as “adverse events.” Refer to the guidance for industry, *Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-

Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.
30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. See guidance for industry, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*. The same applies to PPI and MG.
33. For fictitious examples of labeling in the new format, refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices’ website, <http://www.ismp.org/Tools/abbreviationslist.pdf>

### **SPL Submission**

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); guidance for industry, *Providing Regulatory Submissions in Electronic Format – Content of Labeling*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email [spl@fda.hhs.gov](mailto:spl@fda.hhs.gov) for individual assistance.

### **Integrated Summary of Effectiveness**

Please refer to the guidance for industry, *Integrated Summary of Effectiveness*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

### **CDER Data Standards Reference Guide/Checklist**

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

### **Dataset Comments**

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
- b. Study/protocol number
- c. Patient's treatment assignment
- d. Demographic characteristics, including gender, chronological age (not date of birth), and race
- e. Dosing at time of adverse event
- f. Dosing prior to event (if different)
- g. Duration of event (or start and stop dates)
- h. Days on study drug at time of event
- i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
- j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
- k. Marker for serious adverse events
- l. Verbatim term

2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the *ICH MedDRA Term Selection: Points to Consider* document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.

10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
13. All datasets must contain the following variables/fields (in the same format and coding):
  - a. Each subject must have one unique ID across the entire NDA
  - b. Study number
  - c. Treatment assignment
  - d. Demographic characteristics (age, race, gender, etc.)
14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
17. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

June 3, 2013

Bob Rappaport, M.D.  
Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia, and Addiction Products  
5901-B Amundson Road  
Beltsville, MD 20705-1266

**RE: Information Amendment: pre-NDA Meeting Communication  
Intelliject PIND 112292  
NAI (naloxone auto-injector)  
Investigational New Drug Application  
Serial # 0005**

**Attn: Diana L. Walker, Ph.D., Regulatory Health Project Manager**

Dear Dr. Rappaport:

Please refer to your letter containing FDA's Meeting Preliminary Comments dated May 31, 2013. In that letter the FDA provides preliminary comments to Intelliject's questions for discussion at a Type B meeting pertaining to Intelliject's NAI.

Intelliject has reviewed the FDA's preliminary comments and only requires clarification of 4 questions. Therefore, Intelliject would like to focus the "Discussion of Questions" section of the meeting agenda to the following questions 3, 6, 7, and 20. Additional information for discussion at the meeting is contained in the slides that are provided as an Attachment to this letter, including a reduced number of Intelliject attendees based on the new agenda.

#### **DISCUSSION OF QUESTION 3**

***Question 3.***

*Does the FDA agree that the information planned for inclusion in Submission #1 is sufficient for the FDA to complete its review of the proposed labeling (including voice prompts) for NAI?*

**FDA Response (5/31/2013):**

Based on the proposed submission timeline, we can begin reviewing labeling with Submission #1 and provide feedback as soon as feasible. However, we cannot complete the review of the proposed labeling until all of the relevant data has been submitted (e.g., the clinical study report and datasets for Clinical Bioavailability Study IJ-900DV-03O).

**Additional Background:**

The lead-time for obtaining electronic chips containing the approved voice prompt script is (b) (4). Intelliject is working with suppliers to shorten this lead time however it is (b) (4).

**Clarifying Question 3.A:**

Does FDA agree to provide feedback on the voice prompt script separately as a first priority and prior to submission of the clinical bioavailability study report and datasets?

**DISCUSSION OF QUESTION 6**

**Question 6:**

*Does the FDA agree that there can be no 30-Month Stay of the NAI NDA if no patents claiming the drug, drug product or method of use for the Reference Listed Drug are submitted to FDA's Orange Book Database prior to the first submission (i.e., Submission #1) of the NAI NDA rolling submission?*

**FDA Response (5/31/2013):**

No, we do not agree. We note that a 30-month stay of a 505(b)(2) application will only ensue if a patent covering the reference listed drug is submitted to FDA's Orange Book Database before the date the 505(b)(2) application is submitted to the FDA. The application is considered submitted only after the final submission of the rolling NDA has been submitted and you have informed the Agency that the NDA is complete.

**Clarifying Question 6.A:**

Does FDA agree that the word "date" in "before the date the 505(b)(2) application is submitted" is the date of the final submission of the rolling NDA (along with a letter stating the NDA is complete) and not the date that the final submission is "accepted for filing" by FDA?



**Clarifying Question 20.B:**

[Redacted content]

(b) (4)

Intelliject looks forward to a collaborative and productive discussion at the meeting.

If you have any questions, please contact me at (804) 545-6360 or by email at [ronald.gunn@intelliject.com](mailto:ronald.gunn@intelliject.com) or Glen Kelley at (804) 545-6368 or by email at [glen.kelley@intelliject.com](mailto:glen.kelley@intelliject.com).

Sincerely,



Ronald Gunn  
VP Drug Development and Regulatory Affairs, Intelliject Inc.



# Pre-NDA Meeting

June 4, 2013

Intelliject, Inc. Confidential 2013

# Intelliject Meeting Attendees

Name	Title
Frank Blondino	Director Drug Development
Eric Edwards	Chief Medical Officer
Ronald Gunn	V.P. Drug Development and Regulatory Affairs
Neil Hughes	Chief Commercial Officer
Glen Kelley	Director Regulatory Affairs
Ned Ruffin	General Counsel
Spencer Williamson	Chief Executive Officer

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## Meeting Goals

1. Communicate projected timing of NAI NDA Submissions to FDA
2. Agreement to prioritize the review of the electronic voice prompt script prior to submission of the Clinical Bioavailability study to prevent a delay in commercial manufacturing/launch of NAI.
3. With respect to 30-month stays, confirmation that the word "date" in "before the date the 505(b)(2) application is submitted" is the date of the final submission of the rolling NDA (along with a letter stating the NDA is complete) and not the date that the final submission is "accepted for filing" by FDA.
4. Confirmation of what FDA means by "n-12" and agreement that the shelf-life of NAI can be extended through post-approval submission of real-time stability data in CBE0 supplements to the NDA.
5. Agreement on the additional support required to add (b) (4) to the Indication section of the label and discuss the definition of the (b) (4) population.

# Proposed Meeting Agenda

Topic	Estimated Duration
<b>Introductions</b>	<b>5 minutes</b>
<b>Meeting Goals</b>	<b>5 minutes</b>
<b>Clarification of Responses</b>	<b>15 minutes</b>
<ul style="list-style-type: none"><li>▪ Updated proposed timing for NAI NDA submissions and request for priority review of voice prompts (Question 3)</li><li>▪ Definition of “Submitted” (Question 6)</li><li>▪ (b)(4) shelf-life through post-approval CBE supplements (Question 20)</li></ul>	
<b>Additional support and definition of (b)(4) population (Question 7)</b>	<b>30 minutes</b>
<b>Summary of agreements and action items</b>	<b>5 minutes</b>

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# Updated Proposed Schedule/Content for NAI NDA Submissions

- **Submission #1 (July 2013)**
  - Module 1 (Administrative, proprietary name and labeling)
  - Module 2 (Non-clinical Overview and Summary)
  - Module 3 (Final Human Factors report including use risk analyses)
  - Module 4 (Pre-clinical)
- **Submission #2 (August 2013)**
  - Module 5 (Clinical bioavailability study report and datasets, bioanalytical report)
- **Submission #3 (Q4 2013)**
  - Final submission to complete the NDA

### Question 3 - FDA Early Review of Labeling

**Question 3:**

Does the FDA agree that the information planned for inclusion in Submission #1 is sufficient for the FDA to complete its review of the proposed labeling (including voice prompts) for NAI?

**FDA Response:**

Based on the proposed submission timeline, we can begin reviewing labeling with Submission #1 and provide feedback as soon as feasible. However, we cannot complete the review of the proposed labeling until all of the relevant data has been submitted (e.g., the clinical study report and datasets for Clinical Bioavailability Study II-900DV-03O).

**Background:**

The lead time for obtaining electronic chips containing the approved voice prompt script is (b) (4) (b) (4) Intelliject is working with suppliers to shorten this lead time however it is (b) (4)

**Clarifying Question:**

Does FDA agree to provide feedback on the voice prompt script separately as a first priority and prior to submission of the clinical bioavailability study report and datasets?

## Question 6 – 30-Month Stay of a 505(b)(2)

### Question 6:

Does the FDA agree that there can be no 30-Month Stay of the NAI NDA if no patents claiming the drug, drug product or method of use for the Reference Listed Drug are submitted to FDA's Orange Book Database prior to the first submission (i.e., Submission #1) of the NAI NDA rolling submission?

### FDA Response:

No, we do not agree. We note that a 30-month stay of a 505(b)(2) application will only ensue if a patent covering the reference listed drug is submitted to FDA's Orange Book Database before the date the 505(b)(2) application is submitted to the FDA. The application is considered submitted only after the final submission of the rolling NDA has been submitted and you have informed the Agency that the NDA is complete.

### Clarifying Question:

Does FDA agree that the word "date" in "before the date the 505(b)(2) application is submitted" is the date of the final submission of the rolling NDA (along with a letter stating the NDA is complete) and not the date that the final submission is "accepted for filing" by FDA?

## Question 20 – Shelf-Life

### Question 20:

Provided that the data from these studies remain within product specifications, does the FDA agree that the data will support a (b) (4) -month shelf life for NAI at the time of NAI NDA Submission #3?

### FDA Response:

No, we do not agree. Only 12 months of stability data from the Registration Lots will be available at the time of NAI NDA Submission #3. We expect at least (n-12) months of stability data to be available for review at the time of NDA submission, where n = proposed shelf life.

### Clarifying Questions:

- Does the FDA agree that provided 12 months of real-time stability data are available for review at the final NDA submission and the results remain within product specifications then the proposed shelf-life could be 24 months (i.e., 24-12=12)?

(b) (4)

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## Question 7 – Labeling Changes

### Question 7:

Does the FDA agree with the proposed text in the Indication section and location of updated exemplary opioids in the Dosage and Administration section of the Prescribing Information for NAI as shown in the Target Product Profile in Appendix 10?

### FDA Response:

We will consider the proposed labeling changes during the NDA review. Provide additional support for the proposed changes to the indication statement (i.e., addition of the text (b) (4) and explain how you plan to define this population.

### Clarifying Question:

Does FDA agree that the types of supporting information as presented in the meeting (i.e., market research and published data) would be sufficient for FDA to complete a review of the proposed changes in the indication statement (i.e., addition of (b) (4)

## Supporting Information – Physician’s Perceptions and Behavior

- Most physicians are currently trained that naloxone is for treating an active overdose or for diagnosing a suspected overdose in an unresponsive patient and is to be used by trained healthcare providers only.
- Market research indicates a substantial proportion of prescribers do not believe their patients are at risk of an opioid overdose and would not prescribe NAL.
- The potential for NAL, as an out-of-hospital naloxone product, to save lives depends on changing physician’s current perceptions and behavior.

Adding the language (b) (4) in the Indication Section and possibly providing examples of (b) (4) in another section of the labeling may greatly assist in changing physician’s perceptions and behavior.

# Supporting Information – Physician’s Perceptions and Behavior Based on Physician Interviews

## High Opioid Prescribers

- Accidental overdose from opioids is “a concern”
- 80% explain dangers of opioids to every patient to whom they prescribe opioids
- 100% have patients sign an opioid contract/agreement
- >80% said they would definitely/probably use NAI

N=51; Intelliject Research conducted in 2012 by [REDACTED]

N=15; Intelliject Research conducted 2010 by [REDACTED]

## Moderate Opioid Prescribers

- Accidental overdose from opioids is “not a prominent concern”
- Very few, if any, educate patients on their risk of overdose
- 20% have patients sign an opioid contract/agreement
- Low sense of unmet need – did not see a need for NAI based on their clinical experience

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PMPs – Prescription Monitoring Programs

## Defining the (b) (4) Population

The (b) (4) population should be defined by each physician independently, using their own clinical judgment as to which patients (b) (4) should be prescribed NAI.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANA L WALKER  
06/26/2013