

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208411Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

December 1, 2015

The below REV-SUMMARY-03 (Exclusivity Summary) contains an error. Refer to the corrected review signed on November 30, 2015.

## EXCLUSIVITY SUMMARY

NDA # 208411

SUPPL #

HFD #

Trade Name Narcan Nasal Spray

Generic Name Naloxone hydrochloride, 40 mg/mL

Applicant Name Adapt Pharma Operations Limited

Approval Date, If Known November 18, 2015

### 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)

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

YES  NO

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

#### The study was a bioavailability study:

**The clinical/clinical pharmacology data for this NDA consists of one pivotal comparative bioavailability study (Naloxone-Ph1a-002) conducted in 29 healthy volunteers. In this study, the relative bioavailability from one spray in one nostril (4 mg, 0.1 mL of 40 mg/mL) and one spray in each nostril (8 mg, 0.1 mL of 40 mg/mL in each nostril) was compared to the reference (NDA 16636, Narcan) 0.4 mg of naloxone intramuscular injection.**

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

c) Did the applicant request exclusivity?

YES  NO

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

d) 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?

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:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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

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

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Diana L. Walker, Ph.D.  
Title: Senior Regulatory Health Project Manager  
Date: November 13, 2015

Name of Office/Division Director signing form: Sharon Hertz, M.D.  
Title: Director, Division of Anesthesia, Analgesia, and Addiction Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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  
11/18/2015

SHARON H HERTZ  
11/18/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 208411 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: Narcan Nasal Spray Established/Proper Name: naloxone hydrochloride Dosage Form: liquid spray, 4 mg		Applicant: Adapt Pharma Operations Limited  Agent for Applicant (if applicable): Pacific-Link Consulting
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><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: 11/18/2015</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>January 20, 2016</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR November 18, 2015
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input 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, 505(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.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 3, New Dosage Form  
 (*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 |   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#) )

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: 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 checked="" type="checkbox"/> Other Blog or CDER perspective
❖ 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



❖ 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>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo ( <i>indicate date</i> )	
○ If yes, OC clearance for approval ( <i>indicate date of clearance communication</i> )	<input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> )	
• Date reviewed by PeRC <u>11/4/2015</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) ( <i>include only the completed template(s) and not the meeting minutes</i> )	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) ( <i>include only the completed template(s) and not the meeting minutes</i> )  ( <i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i> )	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	included
❖ 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)	included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 4/20/2015
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Mid-cycle Communication ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A
• Late-cycle Meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) ( <i>indicate dates of mtgs</i> )	6/18/2012
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/18/2015
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/18/2015
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 4 templates, dated 11/18/2015

<b>Clinical</b>	
❖ <b>Clinical Reviews</b>	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) <i>(indicate date for each review)</i>	Filing: 9/3/2015
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ 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>	See CDTL memo
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None Pediatrics: 11/10/2015
❖ 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>	N/A N/A <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 Filing: 9/11/2015 Primary review: 10/22/2015 Addendum review: 11/2/2015
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested Memo: 9/17/2015 Final: 10/30/2015

<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 checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Filing: 8/26/2015 Final: 11/2/2015
❖ 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	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Filing: 8/18/2015 Final: 11/18/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Facilities: 10/14/2015 CDRH Devices: 11/5/2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See OPQ review dated 11/18/2015
<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"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done – N/A ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done – N/A
❖ 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 – no studies required
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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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  
11/23/2015

**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**



**DATE:** 11/16/2015

**TO:** Bunavail (buprenorphine and naloxone) buccal film (new drug application (NDA) 205637)  
Narcan (naloxone) nasal spray (NDA 208411)

**FROM:** CDER Exclusivity Board

**THROUGH:** Sharon Hertz, MD, Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**SUBJECT:** Whether 3-Year Exclusivity for Bunavail (buprenorphine and naloxone) buccal film (NDA 205637) blocks the approval of Narcan (naloxone) nasal spray (NDA 208411)

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**SUMMARY**

This memorandum addresses whether the unexpired 3-year exclusivity for NDA 205637 for Bunavail buccal film (Bunavail), a fixed-combination drug product that contains two active ingredients with the active moieties buprenorphine and naloxone, blocks the initial approval of the 505(b)(2) NDA for Narcan nasal spray (NS), a single-entity drug with only naloxone as its active moiety (NDA 208411).<sup>1</sup>

The Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER), in consultation with CDER's Division of Anesthesia, Analgesia, and Addiction Products (DAAAP or Division) and other components of FDA, concludes that Bunavail's 3-year exclusivity for the conditions of approval of NDA 205637 is tied to the combination of active moieties in Bunavail, and thus recommends that 3-year exclusivity for Bunavail should not block the approval of Narcan NS.<sup>2</sup>

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<sup>1</sup> A drug containing a single active ingredient will be referred to as a single-entity drug and a drug containing two or more active ingredients in a single dosage form will be referred to as a fixed-combination in this memorandum.

<sup>2</sup> This memorandum only discusses whether the 3-year exclusivity for Bunavail should block the approval of the

## I. LEGAL BACKGROUND

### A. Drug Approval Pathways Under the FD&C Act

Section 505 of the Federal Food, Drug & Cosmetic (FD&C) Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs). Because Bunavail and Narcan NS are 505(b)(2) NDAs, the remaining discussion will focus primarily on the 505(b)(2) pathway.

#### 1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, “full reports of investigations” to show that the drug for which the applicant is seeking approval is safe and effective.<sup>3</sup> NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.<sup>4</sup> One basis for FDA not approving a 505(b)(1) NDA is that there is a lack of substantial evidence that the drug product is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.<sup>5</sup>

#### 2. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)<sup>6</sup> amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.<sup>7</sup> The Hatch-Waxman Amendments reflect Congress’s efforts to

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Narcan NS NDA, and does not address the full scope of Bunavail’s exclusivity nor whether Narcan NS is eligible for its own period of exclusivity or the scope of any such exclusivity. Because the two active ingredients in Bunavail are synthetically produced and each contains only a single active moiety, in the remainder of this memorandum we will refer only to the active moiety of these active ingredients instead of using a more cumbersome phrase (e.g., “a single-entity active ingredient containing [name of active moiety] as an active moiety”). This memorandum does not address naturally derived mixtures or other types of products, which may contain one or more active ingredients each of which may contain more than one active moiety.

<sup>3</sup> See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include: a full list of the articles used as components of the proposed drug product; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. *Id.*

<sup>4</sup> See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

<sup>5</sup> See section 505(d)(5) of the FD&C Act.

<sup>6</sup> Public Law 98-417 (1984).

<sup>7</sup> Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s),

balance the need to “make available more low cost generic drugs by establishing a generic drug approval procedure” with new incentives for drug development in the form of exclusivity and patent term extensions.<sup>8</sup> These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.<sup>9</sup>

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the “full reports” requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.<sup>10</sup> Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as: its own studies; published reports of studies to which the applicant has no right of reference; the Agency’s findings of safety and/or effectiveness for one or more previously approved drugs; or a combination of these and other sources to support approval.<sup>11</sup>

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity (NCE),<sup>12</sup> and, in some instances, may describe a drug product with

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dosage form, route of administration, strength, previously-approved conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

<sup>8</sup> See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

<sup>9</sup> See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

<sup>10</sup> Section 505(b)(2) of the FD&C Act provides for approval of an application:

for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

As defined at 21 CFR 314.3, “*Right of reference or use* means the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.”

<sup>11</sup> See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA’s transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

<sup>12</sup> See 21 CFR 314.108(a) (defining *new chemical entity* as “a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the [FD&C Act]”).

substantial differences from a listed drug.<sup>13</sup> When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can *bridge*<sup>14</sup> its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability<sup>15</sup> of the two products, or other appropriate scientific information.

FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process, the 505(b)(2) Draft Guidance, and previous citizen petition responses.<sup>16</sup> FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. FDA's interpretation of section 505(b)(2) avoids requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval, with no corresponding benefit to the public health. In addition, the conduct of duplicative studies may raise ethical concerns because it could subject human beings and animals to medically or scientifically unnecessary testing. The 505(b)(2) pathway permits sponsors and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the drug on which the 505(b)(2) application seeks to rely.<sup>17</sup>

## **B. Exclusivity Under the FD&C Act and Fixed-Combinations**

The Hatch-Waxman Amendments provide incentives for pharmaceutical innovation in the form of 3-year and 5-year NCE exclusivity to protect qualified drugs submitted under section 505(b) from competition from certain 505(b)(2) NDAs and ANDAs for varying periods of time

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<sup>13</sup> In October 1999, the Agency issued a draft guidance for industry entitled "Applications Covered by Section 505(b)(2)" (505(b)(2) Draft Guidance) which states that "[a] 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference." 505(b)(2) Draft Guidance at 3, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>14</sup> The "bridge" in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

<sup>15</sup> Bioavailability data provide an estimate of the amount of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug. See, e.g., FDA's Guidance for Industry: "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" (March 2014) (BA/BE NDA/IND Guidance), at 3.

<sup>16</sup> See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

<sup>17</sup> 21 CFR 314.54(a) states that "[A 505(b)(2)] application need contain only that information needed to support the modification(s) of the listed drug."

depending on the factual circumstances. Although our decision here relates specifically to 3-year exclusivity, we provide background first on 5-year NCE exclusivity for contextual purposes, followed by background on 3-year exclusivity, and then apply the framework to fixed-combinations.

### *1. 5-Year NCE Exclusivity*

The longest and most protective period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity described at section 505(c)(3)(E)(ii) of the FD&C Act.<sup>18</sup> Under this section, a 5-year exclusivity period is provided for a drug “no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [section 505(b)].”<sup>19</sup> This exclusivity generally has been interpreted to prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug.<sup>20</sup> Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

FDA’s regulations at 21 CFR 314.108 implement the statutory exclusivity provisions. Under FDA’s interpretation of the statute, embodied in the regulations, a drug that contains an NCE will qualify for 5 years of NCE exclusivity. If a drug does not contain an NCE, it will not be eligible for 5-year NCE exclusivity, but it may be eligible for 3-year exclusivity.<sup>21</sup>

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<sup>18</sup> A parallel provision can be found at section 505(j)(5)(F)(ii).

<sup>19</sup> Section 505(c)(3)(E)(ii) of the Act provides:

If an application submitted under subsection (b) [of this section] for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) [of this section], is approved after [September 24, 1984], no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) [of this section] before the expiration of five years from the date of the approval of the application under subsection (b) [of this section], except that such an application may be submitted under subsection (b) [of this section] after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) [of this section]. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

See also section 505(j)(5)(F)(ii).

<sup>20</sup> Id. (An applicant may submit an ANDA or 505(b)(2) NDA after 4 years under specific circumstances described in section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act that are not at issue here).

<sup>21</sup> Describing the 5-year NCE exclusivity provisions, Representative Waxman stated:

[T]he amendment provides a 5-year period of exclusive market life for drugs approved for the first time after enactment of the legislation. This provision will give the drug industry the incentives needed to develop **new chemical entities** whose therapeutic usefulness is discovered late when little or no patent life

The Agency’s regulations define *new chemical entity* to mean “a drug<sup>22</sup> that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the [FD&C Act].”<sup>23</sup> *Active moiety* in turn is defined as:

[T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.<sup>24</sup>

FDA’s interpretation of the 5-year NCE exclusivity provisions has focused on the specific chemical structure of the active moiety under consideration;<sup>25</sup> FDA concluded that the term “active ingredient,” as used in the phrase “active ingredient (including any salt or ester of the active ingredient),” refers to the active moiety.<sup>26</sup> FDA adopted a chemical structure-driven

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remains.

130 Cong. Rec. 24425 (1984) (statement of Rep. Waxman) (emphasis added). Representative Waxman contrasted this to 3-year exclusivity (which would be available for drugs that did not qualify for the longer period of exclusivity given to a new chemical entity) as follows:

[A] 3-year period of exclusive market life is afforded to **non-new chemical entities** approved after enactment of the bill which have undergone new clinical studies essential to FDA approval.

Id. (emphasis added). See also 130 Cong. Rec. 23765 (1984) (statement of Sen. Hatch).

<sup>22</sup> In FDA’s guidance for industry entitled, “New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products” (Oct. 2014) (Fixed-Combination NCE Guidance), FDA explains that under its current thinking, the word “drug” in this phrase refers to the drug substance, not the drug product as FDA had previously interpreted the statute. We note that the terms “drug substance” and “active ingredient” are used interchangeably for purposes of this memorandum. See definition of *drug substance* at 21 CFR 314.3(b) and definition of *active ingredient* at 21 CFR 210.3(b)(7).

<sup>23</sup> 21 CFR 314.108(a).

<sup>24</sup> Id.

<sup>25</sup> See, e.g., Abbreviated New Drug Application Regulations, 54 FR 28872, 28897-28898 (July 10, 1989) (“1989 Proposed Rule”).

<sup>26</sup> A recent district court decision has questioned FDA’s interpretation of the 5-year NCE exclusivity provision in the context of a naturally derived mixture containing a new active ingredient with one or more previously approved active moieties. See *Amarin Pharms. Ir. Ltd. v. FDA*, No. 14-cv-00324, 2015 WL 3407061 (D.D.C. May 28, 2015). In the *Amarin* matter, FDA applied its regulation and interpreted the phrase “active ingredient” in the 5-year NCE provision at section 505(c)(3)(E)(ii) to mean “active moiety.” Based on this interpretation, FDA had concluded that the active ingredient of the previously approved naturally-derived mixture at issue in that case contained the same active moiety as in *Amarin*’s drug. FDA had further concluded that *Amarin*’s drug was not eligible for 5-year NCE exclusivity. The court held that, under the circumstances of that case, the statutory language required FDA to determine whether the active ingredient in *Amarin*’s drug had been previously approved, not whether it contained a previously approved active moiety. See *id.* The case has been remanded to FDA for proceedings consistent with the opinion and FDA is considering the best means of implementing the court’s ruling on remand. Although FDA did not appeal, there is currently a pending motion to intervene in that case, filed by Watson, an ANDA applicant that seeks to appeal the *Amarin Pharms* decision. Also, FDA has not yet issued a decision on remand; thus the scope and effect of the court’s ruling have not yet been determined. Given the posture of the *Amarin Pharms* case, until FDA has clarified its interpretation on remand, for ease of reference in this decision, we will interpret the statutory

approach based upon certain reasonable, generally applicable scientific principles regarding the anticipated characteristics of different types of molecules, which can be applied consistently to different types of drugs.<sup>27</sup> Under this approach, the Agency does not need to determine the precise molecule or molecules responsible for the pharmacological action in vivo to determine eligibility for 5-year NCE exclusivity.

Thus, in determining the eligibility for 5-year NCE exclusivity for a single-entity drug, FDA conducts a structure-based analysis on the active ingredient, and if the active ingredient contains an active moiety that the Agency has not previously approved, the drug will be eligible for 5-year exclusivity. Such exclusivity will block any application that contains the active moiety protected by 5-year NCE exclusivity.

## 2. 3-Year Exclusivity

The Hatch-Waxman Amendments also provide for a 3-year period of exclusivity for certain drugs that are not eligible for 5-year NCE exclusivity. The statute and regulations for 3-year exclusivity describe which original NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval by that exclusivity.

For original NDAs, section 505(c)(3)(E)(iii) of the FD&C Act states:<sup>28</sup>

*If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has*

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language “active ingredient” to refer to the active moiety or combination of active moieties of the drug products at issue, not the active ingredient or combination of active ingredients. We note that any ultimate decision on the interpretation of the statutory term “active ingredient” at issue in the *Amarin Pharms* case would not affect the result of this decision because Bunavail is a drug containing a combination of two active moieties and two active ingredients and thus is a distinctly different drug than Narcan NS which contains only one active moiety and one active ingredient. Thus, the active ingredient/active moiety distinction would not affect the outcome here.

<sup>27</sup> See, e.g., Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 FR 50338, at 50358 (Oct. 3, 1994) (“1994 Final Rule”) (concluding that the definition of active moiety should exclude chelates, clathrates, and other noncovalent derivatives because they generally do not affect the active moiety of a drug product).

<sup>28</sup> A parallel provision applies 3-year exclusivity to ANDAs. See section 505(j)(5)(F)(iii) of the FD&C Act.

not obtained a right of reference or use from the person by or for whom the investigations were conducted.<sup>29</sup>

The first clause (italicized) in section 505(c)(3)(E)(iii), often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. As noted in Section I.B.1, in the 5-year NCE exclusivity context, FDA has interpreted the term “active ingredient” in the phrase “active ingredient (including any ester or salt of the active ingredient)” to mean active moiety. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for single-entity drugs that are not eligible for 5-year NCE exclusivity (because they contain an active moiety “that has been approved in another application”) are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA’s implementing regulations further interpret certain aspects of the statutory language regarding eligibility for 3-year exclusivity. Among other things, they define the terms *clinical investigation*,<sup>30</sup> *new clinical investigation*,<sup>31</sup> and *essential to approval*.<sup>32</sup>

The second clause in section 505(c)(3)(E)(iii) (underlined), often referred to as the bar clause, describes which 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity. The Agency’s interpretation of the bar clause and thus a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) generally involves two aspects. One aspect of the scope inquiry focuses on the drug at issue. The phrase “such drug in the approved subsection (b) application” in the bar clause refers to the earlier use of the term “drug” in the eligibility clause. The “drug” in the eligibility clause refers to “a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application,” that is, the drug which includes a previously approved active moiety. FDA interprets this cross reference to mean that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity.<sup>33</sup> Another aspect of the scope inquiry focuses on the new clinical investigations essential to

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<sup>29</sup> See Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4)(iv) (similarly stating that if an application submitted under section 505(b) contains new clinical investigations that were essential to approval and conducted or sponsored by the applicant, the Agency “will not make effective for a period of 3 years after the date of approval of the application a 505(b)(2) application or an [ANDA] for the conditions of approval of the original application . . .”).

<sup>30</sup> “Clinical investigation” is defined as “any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.” 21 CFR 314.108(a).

<sup>31</sup> “New clinical investigation” is defined as “an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.” 21 CFR 314.108(a).

<sup>32</sup> “Essential to approval” means “with regard to an investigation, that there are no other data available that could support approval of the application.” 21 CFR 314.108(a).

<sup>33</sup> See Letter from Janet Woodcock, M.D., Director, CDER, FDA to William H. Carson, M.D., President & CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. and Ralph S. Tyler, Esq., Venable L.L.P. (Oct. 5, 2015) (Docket No. FDA-2015-P-2482).

approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant informs the “conditions of approval” relevant to 3-year exclusivity.<sup>34</sup>

Thus, in the case of an application submitted for a single-entity drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval (i.e., the conditions of approval for which new clinical investigations were essential).

For supplements to approved NDAs, section 505(c)(3)(E)(iv) of the FD&C Act states:

*If a supplement to an application approved under subsection (b) [of this section] is approved after [September 24, 1984,] and the supplement contains reports of new clinical investigations (other than bioavailability [sic] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) [of this section] . . . [(emphasis added)].*

Although the statute and regulations use different words to describe 3-year exclusivity for an original NDA and a supplement to an NDA, FDA has taken a consistent approach to both types of applications in determining eligibility for 3-year exclusivity and scope. The eligibility clause in section 505(c)(3)(E)(iv) (italicized) corresponds to the eligibility clause in section 505(c)(3)(E)(iii) of the FD&C Act, except, among other things, in section 505(c)(3)(E)(iv), the word “supplement” is substituted for the word “application” in section 505(c)(3)(E)(iii). As with an original NDA, a supplement may be eligible for 3-year exclusivity if it contains reports of

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<sup>34</sup> FDA considered, in the context of a single-entity drug, the meaning of the phrase “conditions of approval of such drug in the approved subsection (b) application” in a recent decisional letter regarding whether Astellas’ 3-year exclusivity for its tacrolimus drug, Astagraf XL, blocks approval of Veloxis’ tacrolimus drug, Envarsus XR. See Letter from R. Albrecht, FDA to M. McGuinness, Veloxis Pharmaceuticals, Inc., Jan. 12, 2015 (Veloxis Letter), aff’d Veloxis Pharmaceuticals, Inc. v. FDA, No. 14-cv-2126, 2015 U.S. Dist. LEXIS 77559 (D.D.C. June 12, 2015) (“Veloxis Court Decision”). In the Veloxis Letter, FDA considered both aspects of the scope inquiry in determining whether approval of Envarsus XR was blocked. Although not a subject of dispute, it was clear that in interpreting the phrase “conditions of approval of such drug in the subsection (b) application,” FDA considered the conditions of approval for tacrolimus, which was the single active moiety for the two products at issue. In the Veloxis Letter, FDA repeatedly stated that the exclusivity for Astagraf XL covered “a once-daily, extended-release dosage form of tacrolimus for prophylaxis of organ rejection for use in de novo kidney transplant patients.” FDA did not consider other single-entity drugs that contained a different active moiety in determining whether Envarsus XR’s approval would be blocked. Because the active moiety was the same for the two products at issue, FDA then considered the scope of the new clinical investigations essential to the approval conducted or sponsored by the applicant to determine the “conditions of approval of such drug” and thus the scope of exclusivity.

new clinical investigations (other than bioavailability studies) essential to approval of the supplement that were conducted or sponsored by the applicant submitting the supplement.

The bar clause of section 505(c)(3)(E)(iv) (underlined) describes 3-year exclusivity as blocking approval of a 505(b)(2) application for “a change approved in the supplement.” Although this language is not identical to the phrase “conditions of approval of such drug in the approved subsection (b) application” used in section 505(c)(3)(E)(iii), in determining the scope of exclusivity and which applications are barred, there are likewise two aspects of the inquiry. One aspect of the inquiry focuses on the drug at issue. Under FDA’s longstanding policy regarding which changes are eligible to be approved in a supplement (as opposed to requiring a full, new original application), any change in the active ingredient (and thus any change in active moiety) may only be made through a new, original application, not a supplement.<sup>35</sup> In other words, a change approved in a supplement must be a change in conditions of approval for the same drug (active moiety) approved in the original NDA. Thus, in order to determine that a 505(b)(2) NDA is blocked because it seeks approval for a “change approved in a supplement” during another applicant’s 3-year exclusivity period, FDA interprets the 505(c)(3)(E)(iv) language such that the 505(b)(2) NDA must be for a drug with the same active moiety as the drug with exclusivity.

If the 505(b)(2) application for a single-entity drug seeks approval for the same drug (active moiety) to which exclusivity has attached, then the second aspect of the scope inquiry applies. To determine whether the 505(b)(2) NDA is barred, FDA must also determine what exclusivity-protected change was approved in the supplement. To do so, FDA examines the conditions of approval supported by the new clinical investigations (other than bioavailability studies) that were essential to approval of the supplement. If the 505(b)(2) NDA for a single-entity drug is for the same drug for the same exclusivity-protected change approved in the supplement, it will be blocked.

### 3. *5-Year NCE Exclusivity, 3-Year Exclusivity, and Fixed-Combinations*

The 5-year NCE exclusivity and 3-year exclusivity statutory and regulatory provisions apply not only to single-entity drugs, but also to fixed-combinations. When FDA evaluates a fixed-combination to determine eligibility for 5-year NCE exclusivity, it conducts a structure-based chemistry analysis to determine whether any of the individual active ingredients in the fixed-combination contains an active moiety that has never previously been approved. If the fixed-combination contains an active ingredient that includes a previously unapproved active moiety, that active ingredient is considered an NCE, and 5-year NCE exclusivity attaches to the previously unapproved active moiety. In such a case (with certain exceptions not relevant here) applications for drugs containing that active moiety are barred from submission for a period of 5 years.<sup>36</sup>

As noted in Section I.B, FDA considers eligibility for 3-year exclusivity only if it has determined

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<sup>35</sup> See FDA’s guidance for industry entitled “Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees”, at 3 (Bundling Guidance) (“Every different active ingredient or combination of two or more different active ingredients should be submitted in a separate original application.”).

<sup>36</sup> See Fixed-Combination NCE Guidance at 8.

that 5-year NCE exclusivity is not available. Thus, if after conducting its structure-based chemistry analysis, FDA determines that no active ingredient in the fixed-combination contains an active moiety that has not been previously approved, (i.e., it determines that no 5-year NCE exclusivity will attach), the Agency will then proceed with determining eligibility of the fixed-combination for 3-year exclusivity. In analyzing eligibility for 3-year exclusivity for a fixed-combination, the Agency determines whether the fixed-combination or a change to the fixed-combination is supported by new clinical investigations (other than bioavailability studies) essential to approval of the application for the fixed-combination (or the supplement to the application for the fixed-combination) and were conducted or sponsored by the applicant.

505(b)(2) NDAs are barred from approval by 3-year exclusivity for an original application if they are seeking approval for “the conditions of approval of such drug.” In the case of a fixed-combination, when determining which applications are seeking approval for “the conditions of approval of such drug” and thus have the potential to be blocked, FDA generally focuses its inquiry to applications that contain the same combination of active moieties as in the fixed-combination. This is because the clinical investigations that earn exclusivity must be submitted to the application for the combination, and necessarily support approval of the combination described in the application (or of a change to that combination).<sup>37</sup> Thus, the conditions of approval of *such drug* necessarily encompass the conditions of approval of the particular combination of active moieties of the drug for which the application was submitted and for which new clinical investigations were essential.

Similarly, applications are barred from approval by 3-year exclusivity for a supplement if they are seeking approval for the “change approved in the supplement.” As noted in Section I.B.2, FDA interprets 3-year exclusivity for a supplement to provide the same protection as 3-year exclusivity for an original application. Thus, in determining whether a 505(b)(2) NDA is seeking approval for a “change approved in a supplement” to a fixed-combination and is therefore blocked by 3-year exclusivity for the supplement, FDA similarly focuses its inquiry to applications that contain the same combination of active moieties as in the fixed-combination and examines the scope of the new clinical investigations essential to the approval and that were conducted or sponsored by the applicant. If the 505(b)(2) NDA is not seeking approval for a fixed-combination with the same combination of active moieties as the combination with exclusivity, it is not seeking approval for a change approved in the supplement and therefore cannot be blocked.

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<sup>37</sup> FDA regulations generally require that the combination as a whole be shown to be safe and effective and that each drug in the fixed-combination be shown to contribute to efficacy. It is not adequate for a sponsor to demonstrate only that the individual components are safe and effective. See 21 CFR 300.50.

## II. FACTUAL BACKGROUND

### A. Bunavail<sup>38</sup>

BioDelivery Sciences International's (BDSI's) original NDA for Bunavail buccal film (NDA 205637) was approved by FDA on June 6, 2014. It is a fixed-combination comprising two active moieties: buprenorphine (from the active ingredient buprenorphine hydrochloride (HCl)) and naloxone (from the active ingredient naloxone HCl). Bunavail is formulated as a buccal film that is intended for application to the buccal mucosa, and available in strengths of 2.1 mg buprenorphine/0.3 mg naloxone, 4.2 mg buprenorphine/0.7 mg naloxone and 6.3 mg buprenorphine/1 mg naloxone.<sup>39</sup>

Buprenorphine is both a partial agonist at the  $\mu$ -opioid receptor and an antagonist at the  $\kappa$ -opioid receptor. Buprenorphine was initially approved in 1981 as a parenteral formulation for the treatment of pain (Buprenex, NDA 018401). It was subsequently developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the  $\mu$ -opioid receptor. Moreover, at sufficiently high doses, buprenorphine blocks full opioid agonists from achieving their maximal effects, further deterring abuse of these substances for buprenorphine-maintained patients.<sup>40</sup>

Because it is a partial agonist, buprenorphine also has the potential to precipitate withdrawal symptoms when used by an individual who is dependent on full opioid agonists such as heroin,

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<sup>38</sup> There are other fixed-combination drug products containing naloxone with potential to have unexpired exclusivity. (b) (4)

Zubsolv (buprenorphine and naloxone) sublingual tablets (NDA 204242) is a fixed-combination drug product that contains two active ingredients with the active moieties buprenorphine and naloxone. On August 10, 2015, FDA approved a supplement (S-004) to the Zubsolv NDA. That approval included labeling changes to permit the use of Zubsolv as initial ("induction") treatment of opioid dependence. S-004 was granted 3-year exclusivity by FDA which will expire on August 10, 2018. We do not need to address the full scope of any applicable exclusivity for (b) (4) Zubsolv to recommend that any potential exclusivity for (b) (4) Zubsolv should not block the approval of the Narcan NS NDA. The analysis applicable to Bunavail's 3-year exclusivity, as described in this memorandum, also applies to any applicable exclusivity for Zubsolv (b) (4)

Zubsolv contains a combination of two active moieties (buprenorphine and naloxone), whereas Narcan NS contains only a single active moiety (naloxone). Because Narcan NS does not contain the combination of active moieties approved in (b) (4) Zubsolv, any approval of Narcan NS is not an approval for the "conditions of approval" (b) (4) may have exclusivity or for the "change approved in the supplement" for which Zubsolv has exclusivity. Therefore, we recommend that any applicable exclusivity for either (b) (4) Zubsolv should not block approval of Narcan NS. We need not analyze the second aspect of the scope inquiry as described in Section I.B.

<sup>39</sup> NDA 205637, Summary Review for Regulatory Action (Summary Review) at 1-2 (June 6, 2014). See also Bunavail Product Labeling approved June 6, 2014.

<sup>40</sup> The three sublingual tablet formulations intended for treatment of opioid dependence are NDA 020732 for Subutex (buprenorphine), NDA 020733 for Suboxone (buprenorphine and naloxone), and NDA 204242 for Zubsolv (buprenorphine and naloxone). The sublingual film formulation intended for treatment of opioid dependence is Suboxone (buprenorphine and naloxone) film (NDA 022410), and the extended-release transdermal film formulation is Butrans (buprenorphine) (NDA 021306). Numerous ANDAs have also been approved.

methadone, or oxycodone. The naloxone in Bunavail is expected to precipitate more severe withdrawal symptoms than buprenorphine alone in individuals dependent on full agonists if the formulations are abused and administered parenterally. (More information on naloxone is in Section II.B. below.) Naloxone was first approved in combination with buprenorphine in the sublingual tablet formulation Suboxone (NDA 020733) in 2002. The tablet formulation was designed such that when the product was used as intended, adequate levels of naloxone necessary to precipitate withdrawal would not reach the systemic circulation since it has extremely low oral bioavailability. However, when the product is dissolved, and injected by an individual dependent on full agonists, it provides an additional measure of abuse-deterrence because of its propensity to precipitate more severe withdrawal than buprenorphine.

Bunavail was approved by FDA for the maintenance treatment of opioid dependence on June 6, 2014, as a 505(b)(2) NDA that relied, in part, on FDA's previous finding of safety and effectiveness for Suboxone (NDA 020733) which, as mentioned above, is the sublingual tablet formulation of buprenorphine that also contains naloxone. The Bunavail buccal film is a polymeric film containing the active moieties in two layers – a mucoadhesive layer that contains buprenorphine, and a backing layer that contains naloxone.

No new data on the clinical efficacy of buprenorphine or naloxone were submitted to support the approval of Bunavail. However, because Bunavail is more bioavailable than Suboxone, the amount of both buprenorphine and naloxone in the formulation are lower than in Suboxone. When used as directed, exposures are equivalent. Under conditions of misuse by the intravenous route, the doses are lower. Therefore, the adequacy of the naloxone dose in Bunavail to perform as intended — that is, to precipitate symptoms of opioid withdrawal if the product is dissolved and injected — was supported by a double-blind, placebo-controlled, four-treatment, four-period crossover study to determine the lowest dose of naloxone that would produce a withdrawal response when administered with buprenorphine in opioid dependent subjects (Study LCR-04-01-01). A local tolerability study, Study BNX-201, was also conducted. This study was a 12-week, open-label study in patients who had been maintained on Suboxone tablets at doses between 8 mg and 32 mg for at least 30 days, and who had no baseline abnormalities of buccal mucosa that could affect drug absorption. Based on a specified conversion scheme, patients were switched from Suboxone tablets to the BDSI buccal film as a single daily dose to be administered for 12 weeks.

Bunavail was granted “new product” (NP) exclusivity by FDA which will expire on June 6, 2017. We need not determine the full scope of that exclusivity to recommend that Bunavail's exclusivity should not block approval of Narcan NS as discussed below.

## **B. Narcan NS**

Naloxone is a nonselective opioid receptor antagonist, although it does have greater selectivity for the  $\mu$ -opioid receptor than the  $\delta$  or  $\kappa$  opioid receptor. If naloxone is administered to opioid-dependent subjects, it may produce signs and symptoms of opioid withdrawal. Naloxone was first approved on April 13, 1971, as Narcan (NDA 016636). Narcan and the subsequently approved generic forms of the drug were approved as injectables for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration. These products are indicated for the

complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic opioids, including propoxyphene, methadone and certain mixed antagonist-agonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine. Narcan and the generic versions are also indicated for the diagnosis of suspected or known acute opioid overdose. The indications and usage section of the Narcan labeling also states that

(b) (4)

Naloxone has been approved as a single-entity product and in combination with other opioids like buprenorphine, oxycodone, and pentazocine.

Naloxone is used to reverse the effects of opioids, including in the settings of known or suspected opioid overdose and postoperative opioid depression. The use of naloxone for reversal of opioid overdose in the community has been increasing over the past decade through a number of public health initiatives, generally centered on preventing overdose deaths in people who abuse opioids. These public health programs supplied some combination of a vial or syringe of naloxone with a needle or nasal atomizer device.

Adapt Pharma Operations Limited (Adapt) submitted a 505(b)(2) NDA for Narcan NS (NDA 208411) on July 20, 2015. Narcan NS only contains one active ingredient (naloxone HCl) and one active moiety (naloxone). For approval of this NDA, Adapt is cross-referencing its Narcan NDA (NDA 016636)<sup>41</sup> and is relying on, among other things, published literature. Adapt did not contain any clinical investigations (other than a bioavailability study) essential to the approval of the Narcan NS NDA. Narcan NS would be the first approved single-entity naloxone product that is not an injectable. Narcan NS would be a nasal spray for intranasal administration.<sup>42</sup> Adapt is seeking approval of Narcan NS as an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, which is intended for immediate administration as emergency therapy in settings where opioids may be present. Narcan NS is not a substitute for emergency medical care.

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<sup>41</sup> Narcan injection (NDA 016636) has been discontinued from marketing; however, the Agency determined that Narcan injection was not withdrawn for reasons of safety or effectiveness. FDA, "Determination That DECADRON Tablets and Nine Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness," 74 FR 22751 (May 14, 2009).

<sup>42</sup> On Apr. 3, 2014, FDA approved NDA 205787 for Evzio, a single-use, drug-device combination product containing 0.4 mg naloxone hydrochloride as the drug component. Evzio is an auto-injector designed for use by caregivers and other non-healthcare professionals in the setting of an emergency to reverse opioid overdose. The application was submitted under the 505(b)(2) pathway, relying, in part, on FDA's finding of safety and effectiveness for Narcan (NDA 016636). The studies conducted to support approval of Evzio's NDA included a bioavailability study and human factors studies in which drug was not administered to human subjects. Because the NDA did not contain any clinical investigations (other than bioavailability studies) essential to the approval of the Evzio NDA, the NDA does not qualify for 3-year exclusivity. Therefore, Evzio's NDA does not block approval of the Narcan NS NDA. No other approved single-entity naloxone products have unexpired exclusivity.

### III. DISCUSSION

#### A. Three-Year Exclusivity for Bunavail Does Not Block Approval of the 505(b)(2) NDA for Narcan NS

The issue addressed in this memorandum is whether the 3-year exclusivity for Bunavail (i.e., a fixed-combination containing two active ingredients with two active moieties) will block the approval of the 505(b)(2) NDA for Narcan NS (i.e., a single-entity drug with one active moiety). We conclude that it should not.

Bunavail is a fixed-combination that contains two active ingredients (buprenorphine HCl and naloxone HCl), which contain buprenorphine and naloxone as active moieties. In 2014, at the time of approval of the original NDA for Bunavail, FDA determined that no active ingredient (neither buprenorphine HCl nor naloxone HCl) contained an active moiety that had not been previously approved, and thus no 5-year NCE exclusivity attached. FDA thus proceeded with determining eligibility for 3-year exclusivity and concluded that 3-year exclusivity attached at that time. As explained in Section I.B. above, the conditions of approval of *such drug* necessarily encompass the particular combination of active moieties for which the application was submitted and for which new clinical investigations were essential. The conditions of approval for Bunavail are for the drug containing the combination of active moieties – buprenorphine and naloxone. That exclusivity expires on June 6, 2017. Thus, the exclusivity-protected conditions of approval only bar approval of other 505(b)(2) NDAs for drugs containing the combination of active moieties approved in Bunavail and that otherwise seek approval for the same exclusivity-protected conditions of approval as Bunavail. Because Narcan NS does not contain the combination of active moieties approved in Bunavail, any approval of Narcan NS is not an approval for the “conditions of approval” for which Bunavail currently has exclusivity and no additional inquiry is required. Therefore, we recommend that the exclusivity awarded to Bunavail should not block approval of Narcan NS.<sup>43</sup>

#### B. The Board’s Recommendation that Bunavail’s 3-Year Exclusivity Should Not Block Approval of Narcan NS Is Consistent with FDA Regulations, Congressional Intent, and the Bunavail Approval

The Board’s recommendation that 3-year exclusivity for Bunavail should not block approval of Narcan NS is consistent with the Agency’s regulations regarding fixed-combination drug products and with the approval of the Bunavail NDA.<sup>44</sup> FDA regulations generally require that

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<sup>43</sup> If both Bunavail and Narcan NS contained the same combination of the two active moieties buprenorphine and naloxone, we would need to assess further the scope of exclusivity for Bunavail. We need not reach this aspect of the scope of inquiry here, however, because Bunavail and Narcan NS do not contain the same combination of active moieties. Rather, Bunavail contains a combination of two active moieties, a characteristic that distinguishes it from Narcan NS, which contains only a single active moiety.

<sup>44</sup> The Board’s recommendation here is consistent with the Agency’s decisions on the approvals of NDA 206544 for MorphaBond (morphine sulfate) extended-release tablets and NDA 207932 for Belbuca (buprenorphine HCl) buccal film. The Agency determined that the Oct. 2, 2015, approval of the NDA for MorphaBond was not blocked by any unexpired 3-year exclusivity for Embeda (morphine sulfate and naltrexone HCl) extended-release capsules (NDA 022321). The Agency also similarly determined that the Oct. 23, 2015, approval of the NDA for Belbuca was not blocked by any unexpired 3-year exclusivity for Bunavail (buprenorphine HCl and naloxone HCl) or Zubsolv

the combination as a whole be shown to be safe and effective and that each component (drug) in the fixed-combination be shown to contribute to efficacy.<sup>45</sup> Generally, it is not adequate for a sponsor to demonstrate only that the individual components are safe and effective. The regulation describes “special cases” (or examples) of the general rule regarding when a sponsor must demonstrate that each component (drug) in a combination contributes to the combination’s claimed effect. These examples include when a component is added to the combination: “(1) [t]o enhance the safety or effectiveness of the principal active component;” and “(2) [t]o minimize the potential for abuse of the principal active component.”<sup>46</sup>

Bunavail is one of these special cases. Bunavail was approved as a 505(b)(2) application that relied, in part, on the Agency’s finding of safety and effectiveness for Suboxone (NDA 020733), the sublingual tablet formulation of buprenorphine that also contains naloxone. As noted above, no new data on the clinical efficacy of buprenorphine or naloxone was submitted to support the approval of Bunavail.<sup>47</sup> However, the adequacy of the naloxone dose in Bunavail to precipitate withdrawal if the product is dissolved and injected was supported by a clinical investigation to determine the lowest dose of naloxone that would produce a withdrawal response when administered with buprenorphine in opioid dependent subjects. FDA’s decision to require this study demonstrates that, in this case, the Agency evaluated the drug as a whole, i.e., as a fixed-combination containing two active moieties. Both components are therefore integral to the safety and effectiveness of Bunavail, and it follows that the conditions of approval for Bunavail necessarily include the fact that it contains the combination of buprenorphine and naloxone. This is consistent with FDA’s conclusion that the conditions of approval for Bunavail supported by new clinical investigations relate to the combination of active moieties; and, consequently, any 3-year exclusivity for Bunavail cannot block approval of a drug with only one of the active moieties present in Bunavail.

Further, the Board’s recommendation in this case is consistent with the goals of the Hatch-Waxman Amendments. The Board’s interpretation of the 3-year exclusivity provisions is intended to encourage and reward innovation by protecting a fixed-combination for which new clinical investigations were essential to approval against approval of drugs with the same combination of active moieties for the same exclusivity-protected condition(s) of approval. The Board’s interpretation ensures that 3-year exclusivity for a fixed-combination, if granted, does not block approval of different fixed-combinations (different combinations of active moieties) or of single-entity products. It also ensures that such exclusivity does not block approval of the same fixed-combination (the same combination of active moieties) for condition(s) of approval that were not supported by the new clinical investigations essential to approval. It therefore

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(buprenorphine HCl and naloxone HCl).

<sup>45</sup> See 21 CFR 300.50.

<sup>46</sup> 21 CFR 300.50(a)(2).

<sup>47</sup> For Suboxone, FDA assessed the efficacy of the fixed-combination of buprenorphine and naloxone in addition to evaluating the data or FDA’s findings of safety and effectiveness derived from studies of buprenorphine and naloxone individually. Bunavail in turn relied in part on the Agency’s finding of safety and effectiveness for Suboxone, and thus no new efficacy studies of buprenorphine and naloxone individually were needed to support the approval of the Bunavail NDA.

promotes and protects innovation while also encouraging the development of alternative therapies.

#### **IV. CONCLUSION**

For all of these reasons, the Board recommends that the 3-year exclusivity for approval of NDA 205637 for Bunavail, which contains two active moieties, buprenorphine and naloxone, should not block approval of Narcan NS, which contains naloxone as its single active moiety.

DAAAP concurs with this recommendation.

**Sanjay  
Sitlani -A**

Digitally signed by Sanjay Sitlani -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Sanjay Sitlani -A,  
0.9.2342.19200300.100.1.1=200035  
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Date: 2015.11.16 19:20:55 -05'00'

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/s/  
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DIANA L WALKER

11/18/2015

Entered into DARRTS for the memo signer

**From:** [Walker, Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com)  
**Cc:** [Joyce Reyes \(joycer@pacificlinkconsulting.com\)](mailto:Joyce.Reyes_(joycer@pacificlinkconsulting.com))  
**Subject:** NDA 208411 CMC and Packaging Information Request 04Nov15  
**Date:** Wednesday, November 04, 2015 3:28:16 PM

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Dear Rich,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA:

- 1. Update the relevant sections of the submission to include the newly provided quality information, i.e. Certificates of Analysis for incoming materials (Drug Substance, Excipients etc.) used in the manufacturing of the drug product lots, materials in response to information request. In other words, this information should be moved from Module 1 into Module 3.**
- 2. Revise text on the blister label to add "Do Not Freeze" . We recommend that this statement be added after the statement, "Store at room temperature between (b) (4) " and before the statement, "Protect from light" on the blister label.**

Warm regards,

Diana

Diana L. Walker, Ph.D.  
Sr. Regulatory Health Project Manager  
FDA/CDER/ODE II/DAAAP  
Tel: 301-796-4029  
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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  
11/13/2015

**From:** [Walker Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com); [Joyce Reyes \(joycer@pacificlinkconsulting.com\)](mailto:Joyce.Reyes (joycer@pacificlinkconsulting.com))  
**Subject:** NDA 208411 PMC Information Request and PMR notification 10Nov15  
**Date:** Tuesday, November 10, 2015 1:01:36 PM  
**Importance:** High

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Dear Richard,

The Agency plans to require PMRs for your product, as well as a PMC. This email has two purposes:

1. To inform you of a PMC, and to request that you submit your concurrence to this commitment along with proposed milestone dates. **We request that you submit this information via email by Thursday, November 12, 2015, followed by an official submission to your NDA 208411.**
2. To notify you of two PMRs being required by the Agency for NDA 208411.

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1. The PMC is as follows:

Conduct an adequate leachable safety assessment for the (b) (4) plunger used in your container closure system. This assessment must include leachable data from long-term stability studies testing at least three batches (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for an acute indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples.

Final Protocol Submission: MM/YY

Study/Trial Completion: MM/YY

Final Report Submission: MM/YY

**Please respond with your concurrence and commitment to conduct these assessments, as well as your proposed timetable.**

2. This is a notification of the PMRs that the Agency is requiring. If you have comments or questions, please let me know. These are the two PMRs:

FDA has determined that you are required to conduct the following:

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:
  - a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as  $R(t) = x\%$ , where  $t$  = time and  $x\%$  = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.

- b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
- c. Perform a test to verify the reliability requirements specified in above.

Devices assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.

- Shipping
- Aging
- Storage orientation and conditions
- Vibration handling
- Shock handling (e.g., resistance to random impacts, such as being dropped)

Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.

- Activation orientation
- Environmental temperature

Final Protocol Submission: 02/2016

Study/Trial Completion: 09/2016

Final Report Submission: 11/2016

2. Establish procedures for monitoring reports of failure of the combination product to activate or failure of the combination product to deliver the full labeled dose. Provide annual updates to the NDA record, which contain a detailed analysis of reported device failures (including reported malfunctions that did not result in patient harm), full event narratives, and the results of root cause analysis performed for the reported failure.

Final Protocol Submission: 02/2016

Interim Report: 11/2016

Final Report Submission: 11/2017

Please feel free to contact me if you have any questions.

Warm regards,

Diana

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

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/s/  
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DIANA L WALKER  
11/13/2015

**From:** [Walker, Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com)  
**Cc:** [Joyce Reyes \(joycer@pacificlinkconsulting.com\)](mailto:Joyce_Reyes_(joycer@pacificlinkconsulting.com))  
**Subject:** NDA 208411 Patient Labeling comments 07Oct15  
**Date:** Wednesday, October 07, 2015 12:39:43 PM  
**Attachments:** [instructions-for-use\\_07Oct15.docx](#)

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Dear Rich,

I have received the following comments from our review team. Please respond to these comments with a submission to your NDA 208411:

**The statement, "Use for known or suspected opioid overdose in adults and children" should be included on the following pieces of labeling:**

- 1. Carton labeling: after the statement "Do not test device or open box before use".**
- 2. Blister labeling: after the statement "Protect from light." The size of the proprietary name on the blister may need to be decreased to accommodate addition of this statement.**
- 3. IFU and Quick Start Guide: (See placement and comment in the attached example).**

Warm regards,

Diana

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

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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DIANA L WALKER  
11/02/2015

**From:** [Walker, Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com)  
**Cc:** [Joyce\\_Reyes\\_\(joycer@pacificlinkconsulting.com\)](mailto:Joyce_Reyes_(joycer@pacificlinkconsulting.com))  
**Subject:** NDA 208411 CDRH Office of Compliance Comment 16Oct15  
**Date:** Friday, October 16, 2015 11:46:01 AM

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Dear Richard,

I have received the following comment from CDRH/OC to be conveyed to you. Although you may already know this, they wanted to remind you that because you are complying with 21 CFR 820.30 (Design Controls), you must register and list as a device manufacturer.

**We write to remind you that as an owner or facility involved in the development and/or production of the combination product, you must register and list your product with the FDA. You can find more information at our public website; a direct link is provided here:**

**<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/>**

.

Warm regards,

Diana

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

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/s/  
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DIANA L WALKER  
11/02/2015



NDA 208411

INFORMATION REQUEST

Adapt Pharma Operations Limited  
Attention: Richard Lowenthal, Adapt Pharma Regulatory Representative  
8195 Run of the Knolls Court  
San Diego, CA 92127

Dear Mr. Lowenthal,

Please refer to your original New Drug Application received July 20, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Narcan (Naloxone Hydrochloride) Nasal Spray.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Thursday, October 29, 2015.

1. Provided Certificates of Analyses (CoAs) for all the incoming materials used in manufacturing of all the Drug Product batches included in the submission, i.e. Drug Substance, Excipients, individual components of the Container Closure System components (b) (4) etc. to section 3.2.R.
2. Provide enlarged and readable chromatograms of standard solutions and drug product samples, preferably samples from forced degradation studies for the assay of naloxone HCL nasal spray, and those generated during validation of the following analytical methods.

(b) (4)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

**Steven Kinsley**

-A

Digitally signed by Steven Kinsley -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley -A,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2015.10.26 13:06:50 -04'00'

Steven Kinsley, Ph.D.  
Regulatory Business Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



NDA 208411

INFORMATION REQUEST

Adapt Pharma Operations Limited  
Attention: Richard Lowenthal, Adapt Pharma Regulatory Representative  
8195 Run of the Knolls Court  
San Diego, CA 92127

Dear Mr. Lowenthal,

Please refer to your original New Drug Application received July 20, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Narcan (Naloxone Hydrochloride) Nasal Spray.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Monday, October 19, 2015.

1. Clarify the rationale for [REDACTED] (b) (4)
2. In your August 31, 2015 response to Question #14, you stated that "the length of time between [REDACTED] (b) (4)

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,  
Steven  
Kinsley -A

Digitally signed by Steven Kinsley -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley  
-A,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2015.10.15 15:03:42 -0400

Steven Kinsley, Ph.D.  
Regulatory Business Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** [Walker, Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com)  
**Cc:** [Joyce Reyes \(joycer@pacificlinkconsulting.com\)](mailto:Joyce_Reyes_(joycer@pacificlinkconsulting.com))  
**Subject:** NDA 208411 Container comments 06Oct15  
**Date:** Tuesday, October 06, 2015 11:10:07 AM

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Dear Rich,

I have received the following comments from our DMEPA reviewers concerning the most recent submission dated September 23, 2015, of your draft container labels, in which you responded to prior comments from DMEPA.

The revised container label, blister labeling, and carton labeling are unacceptable from a medication error perspective. Please respond to these comments with a submission to your NDA 208411:

**A. Container label ( (b) (4) two-pack)**

**1. As currently presented, the expiration date is in the format “MMMYY.” We recommend that expiration date be expressed in a standard format, using three-letter text for the month, two-digit numerals for the day (if included), and four-digit numerals for the year, as follows: MMMYYYY (e.g., JAN2015) or MMMDDYYYY (e.g., JAN012015).**

**B. Blister labeling ( (b) (4) two-pack)**

**1. Per the cover letter, the expiration date is in the format “MMMYYY.” See A.1.**

**C. Carton Labeling ( (b) (4) two-pack)**

**1. As currently presented, the expiration date is in the format “MMM/YY.” See A.1.**

**2. As currently presented, the strength (4mg) is included on the side panel, but the usual dose statement is missing. We recommend you consider adding the usual dose statement to the side panel in accordance with 21 CFR 201.55. Since the dose is constant and space permits, we recommend you provide specific dose information on the label. Results from the human factors validation study show five users had uncertainty about the number of doses/though it contained 2 doses.**

Warm regards,

Diana

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

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/s/  
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DIANA L WALKER  
10/06/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 208411

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Adapt Pharma Operations Limited  
c/o Pacific-Link Consulting  
8195 Run of the Knolls Court  
San Diego, CA 92127

ATTENTION: Richard E. Lowenthal, MS, MBA  
Adapt Pharma Regulatory Representative

Dear Mr. Lowenthal:

Please refer to your New Drug Application (NDA) dated July 18, 2015, received July 20, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Naloxone Hydrochloride Nasal Spray, 4mg per 0.1 mL.

We also refer to your correspondence, dated and received July 20, 2015, requesting review of your proposed proprietary name, Narcan Nasal Spray.

We have completed our review of the proposed proprietary name, Narcan Nasal Spray and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 20, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application, contact Diana L. Walker, Ph.D., Regulatory Project Manager in the Office of New Drugs, at (301) 796-4029.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, 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

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/s/  
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TODD D BRIDGES  
10/03/2015



NDA 208411

**INFORMATION REQUEST**

Adapt Pharma Operations Limited  
Attention: Richard Lowenthal, Adapt Pharma Regulatory Representative  
8195 Run of the Knolls Court  
San Diego, CA 92127

Dear Mr. Lowenthal,

Please refer to your original New Drug Application received July 20, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Narcan (Naloxone Hydrochloride) Nasal Spray.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, October 6, 2015.

- 1. In section 3.2.P.2.5 Container Closure System of pharmaceutical development, it was mentioned that LC-MS, GC-MS, inductively coupled plasma/optical emission spectroscopy (ICP-OES) and ion Chromatography were used for analysis of organic and inorganic extractables from (b) (4) stoppers. Provide the location in your NDA submission where the final study report(s) for these extraction results can be found, otherwise submit to the NDA as soon as possible the final extraction report(s) that include details of the analytical methods used, test results of individual extraction studies, and verification / validation of the analytical methods employed in identification of extractables using various solvent indicated, i.e. water, (b) (4) etc.**

- 2. In section 2.3.S.1 Drug Substance: General Information two different (b) (4)**

(b) (4)



3. [Redacted] (b) (4)
4. **Revise the corresponding section of 3.2.P.3 and the Master Batch Record to include visual inspection** [Redacted] (b) (4)  
[Redacted] (b) (4)
5. **Provide the acceptance criterion** [Redacted] (b) (4)  
[Redacted] (b) (4) **Revise the**  
**corresponding section of 3.2.P.3 and Master Batch Record to include the**  
[Redacted] (b) (4) **parameters, and documentation of the test result.**
6. [Redacted] (b) (4)
7. **Update the Master Batch Record to confirm that product specific** [Redacted] (b) (4)  
[Redacted] (b) (4)

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,  
**Steven  
Kinsley -A**

Steven Kinsley, Ph.D.  
Regulatory Business Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Digitally signed by Steven Kinsley -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley -  
A,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2015.09.29 14:11:21 -04'00'



NDA 208411

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Adapt Pharma Operations Limited  
c/o Pacific-Link Consulting  
8195 Run of the Knolls Court  
San Diego, CA 92127

Attention: Richard E. Lowenthal, MS, MBA  
President, Pacific-Link Consulting, Adapt Pharma Regulatory Representative

Dear Mr. Lowenthal:

Please refer to your New Drug Application (NDA) dated July 17, 2015, received July 20, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Naloxone hydrochloride, 4 mg, intranasal spray.

We also refer to your amendments dated April 22, May 29, June 19, July 21, August 6, 25, and 31, and September 8, 2015.

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 January 20, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 30, 2015.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

### **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), patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

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

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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SHARON H HERTZ  
09/16/2015

**From:** [Walker, Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com)  
**Subject:** NDA 208411 Devices Information Request 10sep15  
**Date:** Thursday, September 10, 2015 9:38:52 AM  
**Importance:** High

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Dear Richard,

I have received the following information request from our CDRH (Devices) review team. Please respond as soon as possible with an amendment to your NDA 208411.

- 1. Submission section 3.2.P.5.1 and Table 10 of submission section 3.2.P.1 contain combination product requirements and specifications. You have not provided clear traceability between these combination product requirements and corresponding verification and validation activities. Provide a table that provides traceability between each combination product requirement and the test reports included within your submission, or authorized master files, which verify those requirements.**
- 2. Table 3 of submission section 3.2.P.1 contains a listing of risks/harms associated with your combination product.**
  - a. Provide a summary of the process used to create the listing of harms included in Table 3 and provide information which assures that the process is capable of detecting reasonable hazards associated with the combination product with a high degree of confidence.**
  - b. This table identifies some harms that are considered “unacceptable”. Provide evidence that actions have been implemented to mitigate these risks/harms and demonstrate that those actions are effective at reducing the risk of the event to an acceptable level.**
  - c. Provide further rationale to support your finding of “acceptable” risk for Table 3 harm reference numbers: 2, 3, 4, 10, and 12.**
- 3. The intended use of your product involves the delivery of medication to treat a potentially life threatening condition within use environments that may offer limited opportunity for alternative treatments. As such, the Agency believes that it is essential for your product to perform reliably. Provide a reliability analysis for the subject combination product, including:**
  - a. A statement of any reliability requirements you have established for the subject product.**
  - b. Any test reports or other studies that have been generated to verify reliability**

**requirements.**

Warm regards,

Diana

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

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/s/  
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DIANA L WALKER  
09/10/2015

**From:** [Walker, Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com)  
**Subject:** NDA 208411 Patient Labeling Comments and Track Changes attachments 08sep15  
**Date:** Tuesday, September 08, 2015 10:42:24 AM  
**Attachments:** [NDA 208411 IFU 08sep15.docx](#)  
[NDA 208411 QSG 08sep15.docx](#)  
**Importance:** High

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Dear Richard,

I have received comments from our DMEPA and DMMP (patient labeling) groups concerning your carton and container labels, Instructions for Use, and Quick Start Guide. Please note that these are “preliminary” comments subject to change once the full proscribing information has been reviewed and finalized by the rest of the review teams, however, please respond to these comments by submitting revised labeling. In general, if you agree to the proposed revisions, accept the changes and/or incorporate the requested changes. If you do not agree and have an alternative proposal, make those changes. Please submit your revised carton and container labels, Instructions for Use, and Quick Start Guide as both track changes and clean versions so that the reviewers will be able to quickly see the revisions you have made. (For the IFU and QSG, please submit track changes and clean as Word documents, and you can also include a clean PDF version).

I am including comments in this email below, and also attaching the track changes versions of the IFU and QSG. Note that, in the comments below, there may be some overlap with the comments in the QSG.

A. **Container Label**

- 1. The established name is not at least half the size of the proprietary name. Thus, we request you revise the established name to be in accordance with 21 CFR 201.10(g)(2).**
- 2. We recommend expiration dates be expressed in a standard format, using three letter text for the month, two-digit numerals for the day (if included), and four-digit numerals for the year, as follows: MMMYYYY (e.g., JAN2015) or MMMDDYYYY (e.g., JAN012015).**
- 3. We recommend you change the font color of the strength (b) (4) to black to increase its prominence.**

B. **Blister Labeling**

- 1. See A.2 and A.3.**
- 2. We request you add the “Rx Only” statement in accordance with Section**

**503(b)(4)(A) of the Food, Drug, and Cosmetic Act. Ensure that the “Rx Only” statement does not compete in prominence with the proprietary name, established name, product strength, or route of administration.<sup>2</sup> Consider adding the “Rx Only” statement to the upper middle portion of the label to appear prior to the crease for the peel tab.**

- 3. Consider adding the statement “Peel Here” to the right upper corner. Results from the human factors validation study show four users had trouble opening the package/did not realize it could peel open.**
- 4. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to each individual blister as required per 21CFR 201.25(c)(2). Consider decreasing the size of the dosage form “Nasal Spray” to accommodate addition of the product barcode.**
- 5. We recommend revising the statement, “ (b) (4) ” to, “For use in the nose only” to clarify the correct site of administration. Two participants in the human factors study administered the product in the mouth instead of the nose.**

(b) (4)

D. Carton Labeling-2 nasal spray package size

1. See A.2 and A.3.
2. See C.2 through C.3.
3. We recommend you decrease the font size of the net quantity statement, “Two Pack” so that it does not compete in prominence with the strength statement. Additionally, relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
4. See C.5.

E. Quick Start Guide (QSG)

1. See A.3.
2. Consider increasing the font size of the text within the pictures, if space permits. Results from the human factors validation study show nine users indicated this as an area for improvement.
3. Revise Step 3 of the IFU from, (b) (4)  
 (b) (4) ” to “If the person does not respond (b) (4)  
 (b) (4) .” To include the amount of time to wait prior to administering an additional dose.
4. Add the statement, “Important: For use in the nose only.” to Step 1 to highlight the correct site of administration.

Warm regards,

Diana

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

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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DIANA L WALKER  
09/08/2015

**From:** [Walker Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com); [Joyce Reyes \(joycer@pacificlinkconsulting.com\)](mailto:Joyce.Reyes@pacificlinkconsulting.com)  
**Subject:** NDA 208411 Maternal Health labeling Information Request 27Aug15  
**Date:** Thursday, August 27, 2015 2:52:33 PM  
**Importance:** High

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Dear Rich,

I have received the following information request from our Maternal Health review team. Please respond to the following information request with a submission to your NDA as soon as possible or by September 10.

**On December 4, 2014, the Food and Drug Administration published the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).**

**Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).**

**During our preliminary review of your submitted labeling, you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.**

**Submit the following information on naloxone use in pregnant and lactating women by September 10, 2015:**

- a review and summary of all available published literature regarding naloxone,
- a review and summary from your pharmacovigilance database,
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

**Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.**

Please let me know if you need clarification on this request.

Warm regards,

Diana

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

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/s/  
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DIANA L WALKER  
08/27/2015

**From:** [Walker, Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com)  
**Subject:** NDA 208411 Device Compliance Information Request 24Aug15  
**Date:** Monday, August 24, 2015 3:01:12 PM  
**Importance:** High

---

Dear Rich,

Please respond to the following information request with a submission to your NDA as soon as possible, subject line: Response to Information Request/Product Quality Information.

**1. You provided brief descriptions of how you comply with the Quality System Regulations, in particular, 21 CFR 820.20, 50, and 100. Additionally, you provided a brief description of your change control procedure. It is unclear to us how you have implemented design control for the finished combination product. Submit a summary description of how your design process fulfills the requirements for design and development planning, design input, review, verification, validation, transfer, changes, and design history file.**

**2. We acknowledge that (b) (4) will manufacture the finished combination product. Please refer to 21 CFR Part 4, which describes how manufacturers are to meet the CGMP requirements applicable based on the constituent parts of the combination product. Based on the information in the application and (b) (4) inspectional history, it appears they wish to use a CGMP operating system based on 21 CFR 211. If this is the case, (b) (4) must also demonstrate compliance with the provisions of 21 CFR 820 specified in Part 4 relevant to the product and manufacturing processes. Provide brief summaries of how (b) (4) will comply with the provisions of 21 CFR 820 under Part 4, in particular the management responsibility (21 CFR 820.20), design controls (21 CFR 820.30), purchasing controls (21 CFR 820.50), and CAPA (21 CFR 820.100). You may refer to the Agency's draft guidance on the Current Good Manufacturing Practice Requirements for Combination Products (January 2015).**

Please let me know if you need clarification on this request.

Warm regards,

Diana

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

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DIANA L WALKER  
08/24/2015

From: [Walker, Diana](#)  
To: [Richard L. enthal](#)  
Cc: [Joyce Reyes](#)  
Subject: NDA 208411 : Narcan Nasal Spray packaging informat on request 30Jul15  
Date: Thursday, July 30, 2015 10:57:47 AM

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Dear Rich

I have received the following information request from our DMEPA review team. Please submit this information to your NDA as soon as possible.

**The How Supplied section of the PI includes a (b) (4). We have not been able to locate the carton labeling for (b) (4) in the submission. Please point us to the location of this information within the submission, or submit this information to the NDA.**

You can also submit the information in the email below at the same time if desired.

Warm regards

Diana

---

From: Richard Lowenthal [mailto:richard@pacificlinkconsulting.com]  
Sent: Thursday, July 23, 2015 5:56 PM  
To: Walker, Diana; Skarupa, Lisa  
Cc: Joyce Reyes; Jani, Parinda  
Subject: NDA 208411 : Narcan Nasal Spray - Mock ups and Packaging Photos

Diana / Lisa,

Adapt has shipped samples of the planned packaging presentation for Narcan Nasal Spray to the attention of Diana Walker. Since Diana is out of the office through the 27th, I am ccing Parinda so she is aware that the package will arrive for Diana.

We have limited mock ups right now, but what was sent is as follows:

- A. One (1) Extra Blister loose for viewing and opening.
- B. (b) (4)
- C. One (1) Twin Blister Box containing one PI and two Blister packs.

Photos are below.

As mentioned, the primary packaging is just the Sprayer device with vial (for stability purposes). Each Sprayer is individually blistered. The blister pack also has a label on the back and inside each blister is a Quick Start Guide with instructions for the consumer on how to dose the product. This unfolds to show the main 1, 2, 3.....steps first so that it is very quick to open, read the key needs and proceed.

We will also have three configurations for shipping to customers. (b) (4) One is a box that contains two blisters. Each box has a PI inserted. There is a mini-Quick Start Guide on the box as well so when you open the lid the quick-start guide will be there to review. This allows people to review how to use the product without opening the blister.

The third configuration is just a (b) (4) blisters a PI and a QSG. Again each blister has a QSG as well.

I hope this is helpful. These of course are mock ups and may have some flaws. But I think they will make the planned packaging easy to understand and show how the consumer will be able to quickly access the product and QSG in an emergency.

Regards,

Rich

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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DIANA L WALKER  
08/20/2015

**From:** [Walker, Diana](#)  
**To:** [Richard@pacificlinkconsulting.com](mailto:Richard@pacificlinkconsulting.com)  
**Subject:** NDA 208411 Human Factors Information Request 15Jul15  
**Date:** Wednesday, July 15, 2015 9:23:44 AM

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Dear Rich,

We have started reviewing your Human Factors studies, and have the following information requests. Please send me your responses via email as soon as possible. You can submit the information to your NDA either with the final submission (if you have time to add it), or in a subsequent amendment (subject line of the cover letter can be Human Factors/Response to Information Request).

1. You submitted 2 studies, one that tested giving 2 doses of 2 mg, 2 to 3 minutes apart, and the other that tested giving a single 4 mg dose. The proposed labels and labeling only refer to a 4 mg dose that is administered once.
  - a. Clarify the intent of the first study that tested 2 doses of 2 mg.
  - b. Clarify whether you intend to seek approval for both dosing regimens.
2. The labels reference a Quick Start Guide; however, we have not located this in the submission. We are also not able to locate the Use-Related Risk Analysis. Clarify the location for the Quick Start Guide and the Use-Related Risk Analysis or provide these documents.

Warm regards,

Diana

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

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/s/  
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DIANA L WALKER  
08/20/2015



NDA 208411

**NDA ACKNOWLEDGMENT**

Adapt Pharma Operations Limited  
c/o Pacific-Link Consulting  
8195 Run of the Knolls Court  
San Diego, CA 92127

Attention: Richard E. Lowenthal, MS, MBA  
President, Pacific-Link Consulting, Adapt Pharma Regulatory Representative

Dear Mr. Lowenthal:

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 hydrochloride, 4 mg, intranasal spray

Date of Application: July 17, 2015

Date of Receipt: July 20, 2015

Our Reference Number: NDA 208411

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 September 18, 2015, 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).

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

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

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/s/  
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DIANA L WALKER  
07/20/2015



## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Tele Conference  
**Meeting Category:** Informal

**Meeting Date and Time:** April 22, 2015, 1:15 PM to 1:45 PM (ET)  
**Meeting Location:** Tele Conference

**Application Number:** Pre-NDA 208411  
**Product Name:** Naloxone Hydrochloride Nasal Spray  
**Indication:** Management of suspected (b)(4) Opioid Overdose  
**Sponsor/Applicant Name:** Adapt Pharma Inc. (Adapt)

### FDA ATTENDEES

Eric P. Duffy, Division Director, ONDP/OPQ/CDER  
Julia Pinto, Branch Chief, Branch IV, ONDP/OPQ/CDER  
Ciby Abraham, CMC Lead, Branch IV, ONDP/OPQ/CDER  
Venkateswara Pavuluri, Quality Reviewer, ONDP/OPQ/CDER  
Youbang Liu, Regulatory Project Manager, OPRO/OPQ/CDER  
Diana Walker, Regulatory Project Manager, DAAAP/OND/CDER  
Ryan McGowan, Biomedical Engineer, CDRH  
Richard Chapman, Supervisory Engineer, CDRH  
CDR Alan Stevens, Reliability Engineer, CDRH

### Adapt ATTENDEES

Rich Lowenthal, Adapt Regulatory Representative PLC  
Fintan Keegan, Head Technical Operations, Adapt  
Joyce Reyes, Vice President PLC

### 1.0 PURPOSE OF THE TELE CONFERENCE

Gain information regarding drug product device and provide advice.

### 2.0 DISCUSSION

The Agency started the meeting with an introduction and stated this was an informal meeting.

The Agency proposed to discuss with Adapt the device used to administer naloxone hydrochloride nasal spray. The Agency has determined that the naloxone hydrochloride

nasal spray is a drug/device combination product where the naloxone is the drug and the nasal spray is the device.

The Agency was interested in knowing what Adapt has performed with regards to the evaluation of the particular device in relation to the requirements and specifications determining the device. The Agency stated that this was independent of the DMF information on the characteristics of the product.

Adapt stated that the (b)(4) device is used in commercially available products as well as in current clinical trials. The (b)(4) device that is being used for the naloxone hydrochloride nasal spray is an off the shelf product and was not custom designed. Adapt informed the Agency that they are evaluating the characterization studies with naloxone hydrochloride product utilizing the FDA guidance document on inhalation products.

The Agency was interested in understanding the design selection process that was utilized by Adapt for the nasal device. The Agency wanted to know if Adapt had conducted this type of evaluation and if so what specific characteristics were used in order to define the device to be used.

Adapt informed the Agency that they have done some preliminary evaluations with the regards to the usability of the device with the product. A formal report was not written; however, the data for the selection process was documented and a report could be made available and provided in the NDA.

The Agency was also interested in the design selection from a patient use perspective with regards to performance and reproducibility. The Agency also stated that Adapt would need to address the reliability issue with the device. Adapt stated that they have not seen any reliability issues with this device during the human factor studies that were conducted. Adapt informed the Agency that based on the human factor study, subjects may discharge the product earlier than they should.

The Agency emphasized that per the CDRH regulations and guidance documents that there are compliance standards to keep rigorous documentation with regards to the device, change control, specifications, etc. The Agency wanted to know if Adapt has done any comparison of the device against the DMF with regards to the release of the device. Adapt conducts a review of the overall batch release of the product and device; however, not all of the raw data is scrutinized. Adapt is formalizing a process for the review and batch release of the product and device.

The Agency was interested to know if Adapt conducts independent performance evaluation for the release of the device. At this time, Adapt is in the process of formalizing a specification and are just waiting for additional stability data.

The Agency also wanted to know if Adapt has conducted any Risk/Hazard/FMEA analysis. Adapt stated that this information could be included in the NDA. The Agency

suggested that Adapt create a TOC or list of documents that will be provided in support of the device.

Adapt agreed to gather information that will be available to potentially be included in the NDA and provided to the Agency.

### 3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

### 4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
N/A	N/A	N/A
N/A	N/A	N/A

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YOUBANG LIU  
05/13/2015



**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Tele Conference  
**Meeting Category:** Informal  
**Meeting Date and Time:** April 16, 2015, 4:00 PM to 5:00 PM (ET)  
**Meeting Location:** Tele Conference  
**Application Number:** Pre-NDA 208411  
**Product Name:** Naloxone Hydrochloride Nasal Spray  
**Indication:** Management of suspected (b) (4) Opioid Overdose  
**Sponsor/Applicant Name:** Adapt Pharma Inc. (Adapt)

**FDA ATTENDEES**

Eric P. Duffy, Division Director, ONDP/OPQ/CDER  
Julia Pinto, Branch Chief, Branch IV, ONDP/OPQ/CDER  
Ciby Abraham, CMC Lead, Branch IV, ONDP/OPQ/CDER  
Youbang Liu, Regulatory Project Manager, OPRO/OPQ/CDER  
Diana Walker, Regulatory Project Manager, DAAAP/OND/CDER

**Adapt ATTENDEES**

Rich Lowenthal , Adapt Regulatory Representative PLC

**1.0 PURPOSE OF THE TELE CONFERENCE**

Request samples and ensure the readiness of facilities for inspection.

**2.0 DISCUSSION**

The Agency started the meeting with an introduction and stated this was an informal meeting.

Dr. Duffy explained that the Agency was interested in knowing if any discoloration has been observed with the Adapt naloxone formulation or if the formation of (b) (4) was detected in stability studies. Richard Lowenthal responded that early in the development there was some discoloration observed, but that the original formulation group that supported (b) (4) included EDTA (b) (4) (b) (4). The product has been evaluated on stability as a 10 mg/mL, 20 mg/mL and 40 mg/mL. The 10 mg/mL formulation has more than 18 months stability data and has not shown any discoloration on stability. The clinical lots of 20 mg/mL and 40 mg/mL

have also been evaluated for more than 3 months since manufacture and have not shown discoloration (b) (4).

Dr. Duffy asked if there was any (b) (4) formation. Mr. Lowenthal stated that Adapt has not seen significant amounts of (b) (4) that would exceed the IND limits for degradation. This is why it is not a specified impurity. Dr. Duffy asked if Adapt could specifically assess the amount of (b) (4) if detected and report this with a specification even if at the ICH limit. Mr. Lowenthal said he would discuss this with Adapt.

The Agency also asked if Adapt could submit samples of the product as well as copies of the methods. Mr. Lowenthal said that he believed that was possible and would confirm with Adapt. Mr. Lowenthal noted that he was not sure if there was any of the 10 mg/mL formulation that was used in the original pilot PK study and how much of the clinical lot was left, but that there was large amounts of the registration lots available. Dr. Duffy stated that whatever Adapt could provide for Agency evaluation would be helpful.

The Agency also pointed out that Adapt should be evaluating the product for typical nasal sprayer functionality, including spray particle size and other spray characteristics. Mr. Lowenthal stated that this was being done and that all evaluations would be included in the NDA as per FDA guidelines. Mr. Lowenthal also noted that the (b) (4) DMF includes full testing of the Unit Dose sprayer using model solutions. The Adapt formulation is essentially drug in saline with minor amounts of EDTA and preservative, as such it should be well in the Adapt sprayer. It was confirmed and agreed that testing would be included in the NDA on the specific Adapt formulation being proposed for marketing.

### 3.0 ISSUES REQUIRING FURTHER DISCUSSION

FDA Lab investigation regarding discoloration.

### 4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Samples	Adapt	N/A
Lab investigation	FDA/ONDP and ORT	N/A

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YOUBANG LIU  
05/13/2015



IND 114704

**MEETING MINUTES**

Adapt Pharma Operations Limited  
c/o: Pacific-Link Consulting  
8195 Run of the Knolls Court  
San Diego, CA 92127

Attention: Richard E. Lowenthal, MS, MBA  
President, Pacific-Link Consulting

Dear Mr. Lowenthal:

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

We also refer to the meeting between representatives of your firm and the FDA on March 27, 2015. The purpose of the meeting was to discuss the NDA submission plan for naloxone HCl intranasal with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

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

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

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
  
**Meeting Date and Time:** March 27, 2015, 2:30 p.m. – 3:30 p.m. (Eastern)  
**Meeting Location:** 10903 New Hampshire Avenue  
 White Oak Building 22, Conference Room 1315  
 Silver Spring, Maryland 20903  
  
**Application Number:** IND 114704  
**Product Name:** Naloxone hydrochloride intranasal  
**Indication:** Management of suspected (b) (4) opioid overdose  
**Sponsor/Applicant Name:** Adapt Pharma Operations Limited

**Attendees**

<b>Industry Representatives</b>	<b>Title</b>
Seamus Mulligan	Chairman and CEO, Adapt Pharma
Fintan Keegan	Technical Operations, Adapt Pharma
Matt Ruth	Head of U.S. Operations, Adapt Pharma
Phil Skolnick, PhD, DSc	Director Division DPMCSA, NIDA
Nora Chiang, PhD	Chief Pharmaceutics Branch, DPMCSA, NIDA
Shwe Gyaw, MD	Chief Clinical/Medical Branch, DPMCSA, NIDA
Robert Walsh, RAC	Chief, Regulatory Affairs Branch, DPMCSA, NIDA
Richard Lowenthal, MSc, MBA (MSEL)	PLC Consultant
Joyce Reyes, MSc Regulatory Law,	PLC Consultant
Luana Pesco Koplowitz	PLC Consultant
<b>FDA</b>	<b>Title</b>
Sharon Hertz, MD	Acting Division Director, DAAAP
Steven Galati, MD	Medical Officer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2 (DCP2)
Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, DCP2
Daniel Mellon, PhD	Pharmacology-Toxicology Supervisor
Newton Woo, PhD	Acting Pharmacology-Toxicology Team Leader
Julia Pinto, PhD	Branch Chief, Branch IV, Division of New Drug Products II (DNDPII), Office of New Drug Products (ONDP), Office of Product Quality (OPQ)
Ciby Abraham, PhD	Quality Assessment Lead, DNDPII/ONDP/OPQ
Helen Ngai, PhD	Microbiology, OPF/OPQ
Lisa Skarupa	Regulatory Project Manager, OSE

Vicky Borders-Hemphill, PharmD	Team Leader, Division of Medication Error and Prevention Analysis (DMEPA)/OSE
Hugh Teng	Pharmacy Student
Lisa Basham	Sr. Regulatory Project Manager, DAAAP
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

## 1.0 BACKGROUND

- a. The purpose of this proposed Type B meeting with the Agency is to discuss questions related to the regulatory submission plan, manufacturing and controls, nonclinical data package, and clinical data in support of a planned 505(b)(2) NDA filing for Naloxone hydrochloride intranasal (IN).
- b. Naloxone hydrochloride IN ( (b)(4) 4 mg) is administered in an (b)(4) emergency care or overdose setting in which one or more doses are administered to a person suspected of opioid overdose.
- c. Adapt is planning on filing a 505(b)(2) NDA, referencing Narcan (NDA 016636) as the Listed Product.
- d. A pre-IND meeting was held to discuss the development program for this product on May 24, 2012. Fast Track designation was granted for this product on January 27, 2015.
- e. The Sponsor received the Agency's preliminary responses to the meeting questions on March 25, 2015, via email, and notified the Division that they would like to focus on specific points during the meeting. Those points are added to the meeting discussion below in italics.
- f. The Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

## 2.0 DISCUSSION

*Question 1. Does the Agency concur that Naloxone hydrochloride IN may be filed based on the two completed pharmacokinetic studies as a 505(b)(2) NDA with reference to prior FDA approved NDA and ANDA products as well as literature studies? Adapt plans on referencing both the NDA for Narcan (NDA 016636) and Evzio (NDA 205787) as the Reference Listed Products.*

### **Agency Response:**

**Your proposal to submit a 505(b)(2) NDA for your product, based on the completed relative BA study Naloxone-Ph1a-002 using the final to-be-marketed formulation, appears**

**acceptable. However, you plan to reference both Narcan (NDA 016636) and Evzio (NDA 205787) as the listed products. For a 505(b)(2) application that relies on the Agency's findings of safety and/or effectiveness of a listed drug(s), a scientific bridge via a comparative bioavailability study with each of the listed drugs is required to fulfill the regulatory requirements. You have not described how you plan to rely on Evzio as a listed drug (e.g., the findings, as described in the approved labeling for Evzio, upon which you plan to rely), nor have you described how you will establish a scientific bridge to Evzio. Describe how you plan to rely on Evzio. In addition, if you plan to rely on Evzio as a listed drug, you must conduct a comparative bioavailability study with the approved dosing regimen for Evzio.**

**See "505(b)(2) Regulatory Pathway" comments below.**

#### Discussion

The following statement was received from the Sponsor via email prior to the meeting:

*Adapt does not believe there is any unique data necessary for labeling of the Naloxone IN product in the Evzio approved labeling beyond their PK data. As such Adapt proposes only to reference Narcan (NDA 16,636) and published literature as part of this 505(b)(2) NDA submission.*

*Adapt evaluated two concentrations and doses (2 mg and 4 mg IN) in the pivotal PK study to ensure that at least one dose would be acceptable. But as explained in our cover letter and meeting package, Adapt intends to only market the 4 mg IN dose. Adapt believes that given the wide therapeutic index and safety of naloxone, that it is best to promote a single dose that is most likely to be effective in the vast majority of overdose cases. Since 2 mg IM is considered the most widely used dose and effective in over 80% of cases in a hospital setting, Adapt believes that the 4 mg IN (approximately 2 mg IM) is appropriate for out-of-hospital use. Further, Adapt believes that a single dose in the market is most appropriate to avoid confusion and dosing decisions (that require repeat dosing) by lay-persons in an emergency medical situation. Thus, Adapt would appreciate confirmation from FDA at the preNDA meeting that the 4 mg IN is the most appropriate dose for submission of the planned 505(b)(2) NDA.*

The Agency acknowledged the points made by the Sponsor, and asked the Sponsor to clarify whether the formulation of the pivotal BA/BE study will be the same as the commercial batches. The Sponsor confirmed that the formulation is the same.

*Question 2. Does the Agency agree with the proposed labeling, including the Prescribing Information, Instructions for Use and Quick Start Guides for caregivers that are intended for submission in support of the Naloxone hydrochloride IN?*

#### **Agency Response:**

**The Prescribing Information, Instructions for Use, and Quick Start Guides for caregivers will be reviewed in detail during the NDA review. However, we recommend you look at**

**already-approved naloxone products intended for use in the community to get an idea of our current thinking on how these products should be labeled. Also, refer to our response to Question 5.**

Discussion

There was no further discussion of these comments.

*Question 3. Does the Agency concur that the results of the Naloxone-Ph1a-001 and Naloxone-Ph1a-002 pharmacokinetic studies support the proposed single-spray doses of 2 mg and 4 mg planned for submission of the Adapt Naloxone hydrochloride IN in the 505(b)(2) NDA and Prescribing Information (Labeling)?*

**Agency Response:**

**We agree that the results of your pharmacokinetic studies are acceptable to support submission of an NDA for both the 2 mg and 4 mg doses of your proposed product. However, the data will be evaluated during the NDA review to determine if they support the application's approval. You must also establish a scientific bridge to Evzio if you intend to rely upon any of the Agency's previous findings for that product (refer to our response to Question 1).**

**You state in the briefing package that "Adapt and NIDA believe that the 4 mg IN single spray dose is the most appropriate and prudent safe dose to ensure efficacy is achieved with a single-spray administration and which will most effectively avoid the need for excessive repeat dosing that may result in a failure to rescue overdose victims." (b) (4)**

**As detailed in the pre-IND meeting minutes dated June 18, 2012, the following information is required to support the bioanalytical assay and validation for your pivotal clinical pharmacology study:**

- **Note the minimum requirements for retention of BA and BE samples. Refer to Guidance for Industry: *Handling and Retention of BA and BE Testing Samples*, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>.**
- **Maintain adequate record keeping to allow for complete reconstruction of all study-related events (clinical and bioanalytical, including method validation).**

**For complete details, refer to our post-meeting comments provided in the Pre-IND meeting minutes dated June 18, 2012.**

Discussion

See discussion under Question 1.

*Question 4. The results of the Naloxone-Ph1a-001 and Naloxone-Ph1a-002 pharmacokinetic studies demonstrated that Naloxone hydrochloride IN was well tolerated and did not result in any significant irritation of the nasal mucosa or other side effects. Given there are no signals of any side effects that are unique to IN dosing, does the Agency agree that the safety profile for purposes of the Prescribing Information (Labeling) can be based on the currently approved injectable naloxone products (e.g. Narcan and Evzio) as part of this 505(b)(2) NDA?*

**Agency Response:**

**The determination of safety for your product will be a review issue, as will the determination for the adequacy of the submitted data to support a bridge to the Agency's previous findings for the reference product. However, we agree that the safety profile will likely be supported, to a large extent, by the safety findings for your reference product, as described in approved labeling, and be further supported by the safety data from your clinical development program and your review of the published literature documenting any new clinical information for Narcan since its approval in 1971 (e.g., adverse events, overdose).**

**You must provide additional data or justification to assure that the higher exposure seen with your product, as compared to the reference product, does not represent a safety concern. Considering naloxone has a relatively large therapeutic index and that the concern would be greater for delivering less naloxone than the reference product, this justification could be based on literature and leveraging existing information from your reference product (i.e., higher approved doses and maximum repeat doses for the reference product).**

**Also refer to our response to Question 1, as we are unclear on how you plan to rely upon the Agency's previous findings for Evzio.**

Discussion

There was no further discussion of these comments.

*Question 5. Adapt is completing Human Factors and Label Comprehension studies for the Instructions for Use labeling (Quick Start Guide). The results of a pilot study are included in this preNDA meeting package. The protocol synopsis for the pivotal Human Factors and Label Comprehension study is also provided in this meeting package and the results will be included in the planned 505(b)(2) NDA. These studies are intended to confirm that average lay persons and caregivers can adequately understand the Instructions for Use and Quick Start Guide. Does the Agency agree that the now ongoing pivotal Human Factor and Label Comprehension study is adequate to support review of the proposed labeling for Naloxone hydrochloride IND?*

**Agency Response:**

**The results of your “pivotal” human factors and label comprehension study will be adequate to support submission and review of the product user interface, including labels and labeling, from a usability perspective. Ensure that your study results report includes the following:**

- 1. A summary of your results and analysis from your formative study**
- 2. A discussion of changes made to your product after the formative study, including how the results from the formative study were used to update the user interface and use-risk analysis**
- 3. An updated use-related risk analysis**
- 4. The complete human factors validation study protocol that includes the following essential elements:**
  - i. Intended users and rationale for how test participants are representative of the essential demographics of the intended users**
  - ii. Uses, use environment, user interface**
  - iii. Training (if applicable)**
  - iv. User Tasks, task prioritization, and definition of task failures in terms of clinical impact**
  - v. Data collection [observational (pass/fail, close calls operational difficulties, interview data, etc.) and analysis]**
- 5. Intend-to-market labels and labeling (including Quick Start Guide) that were tested in the pivotal human factors studies**
- 6. If additional changes are made to the user interface after completion of the pivotal human factors studies, provide a side by side comparison document that outlines all of the changes made and why**
- 7. Three intend-to-market samples of product**

**Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available at,**

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm094460.htm> .

Note that we have also published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors and product design.

1. *Applying Human Factors and Usability Engineering to Optimize Medical Device Design (Draft)*, available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf>
2. *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft)*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>
3. *Safety Considerations for Product Design to Minimize Medication Errors (Draft)*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

#### Additional Comments

1. If you intend to have a proprietary name for this product, the appropriate regulatory pathway for a Request for Proprietary Name Review is through a separate submission to your IND/NDA. Acceptability of the proposed proprietary name requires a promotional and safety assessment. We will perform such an assessment once we receive a formal request for review from you. Once the assessment is complete, we will issue a letter with the final determination for your proposed Proprietary Name. The content requirements for such a submission can be found in the draft guidance for industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>).
2. Consider packaging two intranasal spray units together in one blister pack for distribution in the event a second dose is warranted during an emergency situation (e.g., the caregiver accidentally discharges the device prior to placement in the nostril, a second dose is required before medical care becomes available). To ensure that important product information is provided with each intranasal spray unit, we recommend that each blister pack, containing two intranasal spray units, is packaged in a carton along with the instructions for use. In the event that the instructions for use become separated from the carton, we recommend that the instructions for use be printed on the carton. Several cartons may then be packaged

**in box. Ensure that each individual spray unit contains the minimum amount of information required per 21 CFR 201.1 on the container label and includes the following:**

- **Proprietary name**
- **Established name**
- **Product strength**
- **Identifying lot or control number**
- **Name of manufacturer, packer, or distributor of the drug**
- **Expiration date**

Discussion

The following statement was received from the Sponsor via email prior to the meeting:

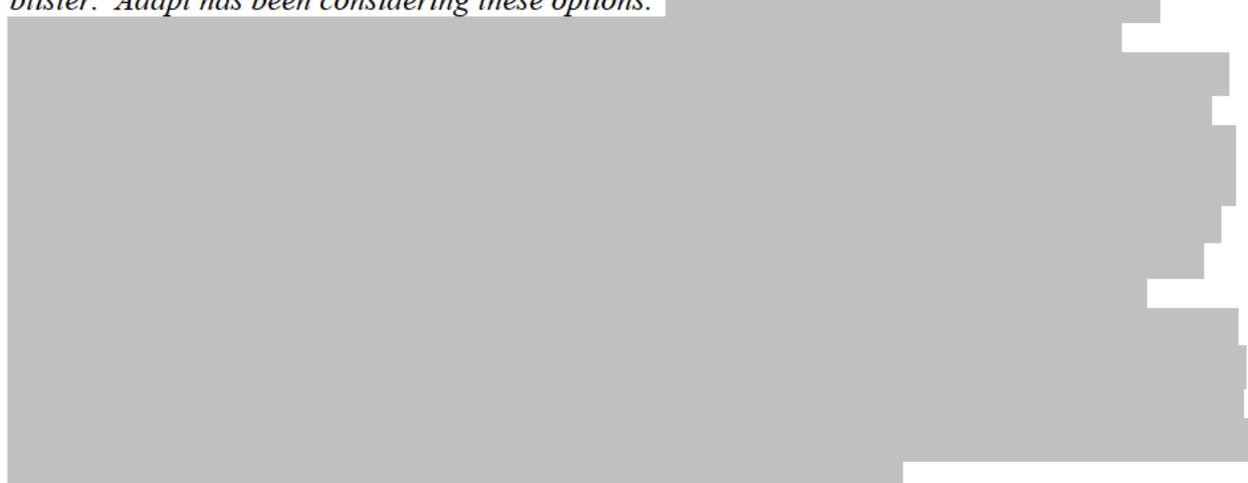
*Regarding Comment 1, Adapt is aware and is completing assessment of possible names with a plan to file the proposed Proprietary Name to the IND with appropriate supporting studies. Depending on the timing of the final NDA submission, Adapt believes that this initial submission will allow the process to be initiated but may not provide time for FDA to complete the review before the NDA submission. As such Adapt wants to confirm that FDA agrees to this interim submission to the IND to start the process even if only a couple months prior to the NDA filing.*

The Agency stated that the timeframe for review of a Proprietary Name is 180 days when submitted to the IND and 90 days when submitted to the NDA. The Agency confirmed that the Sponsor can submit a Proprietary Name request to both the IND and the NDA, and that any comments on the name will be communicated as soon as possible.

The following statement was received from the Sponsor via email prior to the meeting:

*Regarding Comment 2, Adapt notes FDAs suggestion to package two intranasal devices in one blister. Adapt has been considering these options.*

(b) (4)



The Agency stated that the Sponsor must submit an LOA for the device, and that the LOA should be submitted as soon as possible as the device must be reviewed if it is not already 510K cleared. The Sponsor agreed, and stated that they will submit an LOA for the device DMF. The device is an (b) (4) product and has been used with other approved drug products.

The Agency stated that packaging two blister units for marketing is recommended, because of a possible mistake by the user or to permit redosing if there is a potential delay in getting the person who overdosed under professional medical care. (b) (4)

(b) (4)  
The Sponsor conducted a qualitative study last year that is complete, and is currently conducting the validation studies. The validation study using two devices is completed (b) (4)  
(b) (4) The preliminary results show that, while the endpoints are generally good, people had problems waiting 2 to 3 minutes to determine whether a second dose was required, and many used a second dose right away if it was available. The Sponsor also pointed out that, after the use of one unit, there would only be a single unit available to treat any future overdose.

The Agency told the Sponsor to submit their rationale for the proposed packaging configuration with the NDA submission.

Question 6. *Does the Agency concur with the plan to reference nonclinical studies to prior FDA approved naloxone containing products, as well as published literature studies is adequate for the planned 505(b)(2) NDA?*

**Agency Response:**

**Yes, we concur. We note that usually, as naloxone is not approved for the intranasal route of administration, local tolerance studies in two species of adequate duration would be required to support your NDA. However, as there is considerable clinical experience with intranasally administered naloxone and your formulation does not appear to contain novel excipients, in lieu of animal studies or literature references to those animal studies, you may submit your assessment of local tolerance based on clinical monitoring of local tissues.**

**Additional Nonclinical Comments**

- 1. 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(R2) qualification thresholds along with a 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.**

**Refer to guidance for industry: *Q3A Impurities in New Drug Substances*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>**

**and**

**guidance for industry: *Q3B (R2) Impurities in New Drug Products*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>**

- 2. The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As 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 labeling.**
- 3. 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 published 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.**
- 4. New excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>. As noted in the guidance, “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).**
- 5. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A and ICH Q3B(R2) 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. In this case, 14 days for an acute indication.**

Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf>.

6. **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.**
7. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to ICH M7 guidance document titled: *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying or controlling these impurities. This guidance is available at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Multidisciplinary/M7/M7\\_Step\\_4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf). Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.**
8. **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. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. The choice of solvents and conditions for the extraction studies should be justified. The**

results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, you should still evaluate the drug product over the course of your stability studies and base the final safety assessment on the levels of leachables identified 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 the FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf> and the FDA guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure for a chronic indication or be adequately qualified for safety. From a genetic toxicology perspective, we will allow up to 120 mcg/day for an acute indication for most potentially genotoxic impurities. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

#### Discussion

There was no further discussion of these comments.

Question 7. *Does the Agency concur that, for the planned 505(b)(2) NDA, the proposed specifications for the naloxone hydrochloride IN product are sufficient to properly control the product release and shelf life quality?*

#### **Agency Response:**

The proposed release and shelf-life specifications include the appropriate tests and acceptance criteria for the drug product. For more information, refer to guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products- Chemistry, Manufacturing and Controls Documentation*, available at,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>.

The proposed specifications for release and stability seem reasonable. However, we have the following comments:

1. A second identification test is required.
2. Ensure that the specification for benzylkonium chloride is the same at release and stability.
3. The specification for disodium edetate seems (b) (4) the limit or provide data in the NDA to justify this specification.
4. Testing for related substances should include testing of all known individual impurities, including testing for the (b) (4) impurity.

Your drug product specifications currently meet ICH Q3B(R2) qualification thresholds and are acceptable.

#### Discussion

The Agency stated that, in the NDA submission, numerical data for specifications are required. Text terms such as “comply” are inadequate, and specific numerical data must be provided. The Sponsor stated that they understood this requirement.

#### Post Meeting Note:

The response to Question #7 from the FDA is revised as follows:

**The proposed release and shelf-life specifications should include microbial testing and the appropriate tests and acceptance criteria for the drug product according to the FDA guidance: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products- Chemistry, Manufacturing and Controls Documentation*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>.**

**Question 8.** *Does the Agency agree with the in-use studies completed to support the use of the (b) (4) single dose nasal sprayer in combination with the Naloxone hydrochloride IN product?*

#### **Agency Response:**

**The selected studies appear reasonable. However, additional studies may be required upon evaluation of the submitted data in its totality.**

**For additional guidance, refer to guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls***

**Documentation, available at,**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>.

Discussion

There was no further discussion of these comments.

*Question 9. Adapt plans on filing the proposed 505(b)(2) NDA based on two lots of 10 mg/mL product with data through 24 months, two clinical lots of commercial product (one each 20 mg/mL and 40 mg/mL) with data through 6 months, and 6 registration lots (three each 20 mg/mL and 40 mg/mL) with data through 3 months. For all lots both long-term and accelerated conditions will be provided, including inverted samples on the clinical and registration lots. Adapt intends on filing additional stability data for both accelerated and long-term conditions prior to approval of the planned 505(b)(2) NDA to support the proposed expiration date on the product. Does the Agency agree with the proposal to file the initial 505(b)(2) NDA with the available stability data outlined above given the known stability profile of the similar aqueous formulations of IM and IV naloxone hydrochloride currently approved by FDA for commercial use?*

**Agency Response:**

**We do not agree with your proposal. Per ICH Q1A(R2), at least 12 months of data under long-term storage conditions and 6 months of data under accelerated conditions is expected at the time of submission for at least three batches of drug product, stored in both the upright and inverted positions. Refer to guidance for industry: *Q1A(R2) – Stability Testing of New Drug Substances and Products*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073369.pdf>**

**Also note that any identified leachables must be monitored during long-term stability studies.**

**We note that you have conducted an extractables study. A final study report for the extractables study must be submitted to the NDA that provides calculations of maximum levels of extractables a patient may be exposed to under a worst-case scenario. We acknowledge your justification for not conducting a leachables assessment but cannot comment on its adequacy until we review the results of the extractables study. We always recommend that sponsors conduct leachables assessments with the drug product throughout the product's shelf-life and provide a toxicological risk assessment for all leachables detected above the Toxicological Threshold of Concern (TTC) of 5 mcg/day.**

Discussion

The following statement was received from the Sponsor via email prior to the meeting:

*Adapt understands that the standard ICH stability requirements for submission of a new drug product are for 3 lots of drug product (pilot and/or commercial scale) with 12*

*months stability. However, given the urgent medical need for an approved GMP manufactured Naloxone IN product at a dose that is appropriate for out-of-hospital use by lay persons, Adapt believes that some exceptions are warranted. Further, Narcan (naloxone in saline) is relatively stable with an expiration period of over 36 months without significant degradation. The Naloxone IND formulation is similar with only preservative (b) (4) added, which is not anticipated to have any negative impact on stability and current stability data indicate it shows no measurable degradation of the API.*

*Adapt has conducted stability on three concentrations of Naloxone Intranasal with the same basic formulation. The lowest concentration, worst case product, has over 24 months of (b) (4) data that will be available for the submission. Further, 6 months (b) (4) and Accelerated stability will be available on one lot of 20 mg/mL and one lot of 40 mg/mL at both upright and inverted conditions. The registration batches which are 3 lots of 20 mg/mL and 3 lots of 40 mg/mL, will have 3 months of stability at (b) (4) and Accelerated in both the upright and inverted conditions at time of submission. All of these studies demonstrate that the Naloxone Intranasal product is very stable.*

*Adapt believes that the cumulative data is adequate to ensure that the stability profile of the Adapt Naloxone IN product is similar to, or better than, Narcan for Injection. This approach can also be supported by literature stability data on various formulations of naloxone in solution that demonstrate the lack of any significant risk of instability. Given the critical need for GMP manufactured Naloxone IN with a dose that will be adequate to treat the majority of overdose cases in an out-of-hospital emergency situations, Adapt believes that some exception to standard requirements is warranted.*

*Adapt proposes to file in June with the proposed stability package, and supplement with additional data during the NDA review that should support an expiration date of (b) (4) months at time of launch.*

The Agency stated that, while it is understood that this is a very important product for the public health, data must be submitted to support the expiry. The Agency normally requests 12 months of data to look at the trends in degradants and impurities, but given the public health benefit and what is already known about naloxone is willing to accept less than usual if some conditions are met. The Agency is concerned that naloxone (b) (4) is a specified impurity (b) (4). The Agency requested that the Sponsor submit all available data that includes testing for the (b) (4) impurity, including a full report of the original data, and re-testing of the 10 mg/mL batches as well as any other available batches of 20 mg/mL and 40 mg/mL strengths, at the current time point using the (b) (4) specifications the Agency has requested. Additionally, the Sponsor must submit the validated HPLC analytical method for determination of (b) (4) testing into future release and commercial testing. The Sponsor stated that, although (b) (4) was measured, the reason they had not included the test data in the submission is that it is below the level of detection. However, the Sponsor agreed to submit the original data as well as re-testing the batches at current time points. The Sponsor stated that they have worked with two formulations, and 20 mg/mL and 40 mg/mL, but that they will market only the 40 mg/mL. The 10 mg/mL is the same

formulation, only differing in concentration. In June, at the time of the proposed NDA submission, the Sponsor will have stability data from two clinical batches at 6 months and three registration batches at 3 months. By July, the clinical batches will have 9 months and by August the registration batches will have 6 months of stability data. The Sponsor agreed to send the Agency a table containing all of the batches and a schedule of available stability data. The Agency agreed to review this information and determine the best possible expiry that can be granted.

The Agency asked the Sponsor to clarify whether extractables/leachables are being monitored on stability. The Sponsor said they are not monitoring extractables/leachables, but will submit a risk assessment for the extractables. The Agency stated that Sponsors are encouraged to monitor for extractables/leachables on stability, and recommended that the Sponsor submit any known data concerning the stopper extractables.

The Agency asked the Sponsor to clarify the role of disodium edetate in the formulation, and why they are monitoring for it. The Sponsor stated that in the original batch there was (b) (4) the disodium edetate was added. The Sponsor agreed to send further background information on the history and role of disodium edetate in the formulation to the Agency. The Agency stated that, if the data from the current batches (b) (4) then an appropriate expiry will be determined. (b) (4)

#### Post-Meeting Note

The Sponsor sent the following clarification after the meeting via email on April 8, 2015:

*We followed up and as mentioned in the meeting the EDTA was added* (b) (4)

(b) (4)

Agency Response: Provide all available data to the NDA, including any reports regarding the (b) (4) solution and (b) (4) levels.

#### Additional Clinical Comments

**Per our teleconference on February 24, 2015, your product will trigger the requirements under PREA, and your pediatric study plan (PSP) must describe how you plan to satisfy the requirements under PREA. We believe that products containing naloxone for use in an out-of-hospital setting for opioid overdose should be available for all pediatric age ranges. Given the wide safety margin for naloxone, the dire clinical consequences of not treating an opioid overdose, and the difficulty of delivering pediatric weight-based dosing for naloxone (as is currently recommended in Narcan labeling) in an out-of-hospital setting, a fixed dose as you have proposed for your product may be appropriate for all age ranges, including those in pediatrics. There is a great public health need for this product to be made available to all pediatric patients as a result of the risk of accidental opioid overdose, and misuse and abuse of opioids leading to overdose in the pediatric population; and appropriate pediatric labeling should address use in those settings.**

**However, studying naloxone products in pediatric patients poses several challenges. In children, as in adults, it is not ethical to conduct an efficacy study in the setting of opioid overdose using an unapproved route of administration for naloxone when life-saving, already-approved products are available. Nor would it be ethical to intentionally overdose subjects with opioids in a controlled setting. Therefore, for adults, sponsors of naloxone products are required to demonstrate that naloxone pharmacokinetics are equal to or exceed that of an approved route of administration for naloxone (i.e., Narcan) in healthy volunteers. However, pediatric studies, similar to what is required in adults, cannot be conducted using healthy children, as such studies would involve more than minimal risk to subjects without presenting the prospect of direct benefit to the individual subjects.**

**You may wish to approach addressing the requirements under PREA by providing a justification (e.g., from literature, published clinical practice guidelines, approved Narcan labeling) for why your product, containing a fixed dose of naloxone, is acceptable for all pediatric age ranges to support the safety and efficacy of the proposed dose in pediatric patients and the pediatric labeling for your product. Although we do not expect the pediatric nasal mucosa to be sufficiently different from adults or to adversely impact the systemic absorption of naloxone, the total amount of fluid that may be instilled into a smaller nasal cavity is anticipated to be less. As part of the justification, you must provide data for why the volume of drug product contained in your product is appropriate for the nasal cavities of the entire pediatric age range. Otherwise, you must develop an age-appropriate formulation for all pediatric age ranges, supported by appropriate pharmacokinetic studies in adults, and consider later substituting that formulation in all age ranges, including adults, to avoid dosing confusion during an emergency situation.**

**Refer to “PREA Requirements” below.**

Discussion

There was no further discussion of these comments.

### **3.0 ADDITIONAL COMMENTS**

#### **4.0 General pre-NDA Comments**

#### **PREA REQUIREMENTS**

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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. The PSP should be submitted in PDF and Word format.

In addition, your PSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or

email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### Discussion

The Sponsor stated that they have submitted their iPSP to the IND, and that they plan to incorporate any comments from the Division into the PSP submission to the NDA. The Sponsor also stated that, as a point of information, there is no information in the literature on neonates that they have been able to locate, but that there is some information on infants, which they plan to submit with their proposal.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### Discussion

There was no further discussion of these comments.

## **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."

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.				

Discussion

There was no further discussion of these comments.

**505(b)(2) REGULATORY PATHWAY**

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, in part, 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, in part, 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, in part, 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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>

2. Example: NDA XXXXXX “TRADENAME”	Previous finding of effectiveness for indication X
3. Example: NDA YYYYYY “TRADENAME”	Previous finding of safety for Carcinogenicity, labeling section XXX
4.	

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 Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

#### Discussion

There was no further discussion of these comments.

#### **Office of Scientific Investigations (OSI) Requests**

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 those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to 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 (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

#### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

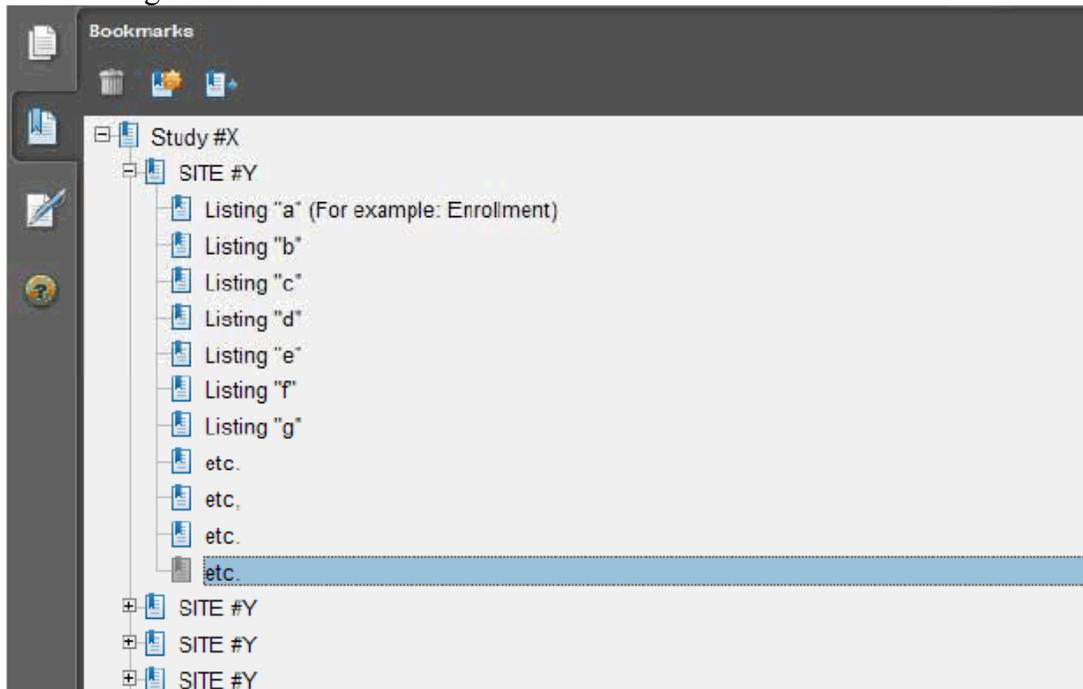
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number

- b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
    - a. Number of subjects screened at each site
    - b. Number of subjects randomized at each site
    - 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 pivotal clinical trials:
    - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
    - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
    - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
  4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
  5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

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

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)

- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - 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, including a 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 testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing

Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> ) for the structure and format of this data set.

Attachment 1  
**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.

<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

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)

Discussion

There was no further discussion of these comments.

**5.0 ACTION ITEMS**

- a) The Sponsor agreed to send the Agency a table containing all of the drug product batches with a schedule of stability time points. The Agency agreed to review this information and determine the best possible expiry that can be granted.
- b) The Sponsor agreed to send further background information on the history and role of EDTA in the formulation to the Agency.
- c) The Agency agreed to review and provide comments on Proprietary Name submissions received to the IND or NDA according to the 180-day or 90-day review time lines, respectively.

**6.0 ATTACHMENTS AND HANDOUTS**

None.

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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  
04/20/2015



PIND 114704

**MEETING PRELIMINARY COMMENTS**

Lightlake Therapeutics, Inc.  
86 Gloucester Place,  
Ground Floor Suite  
London, W1U 6HP, UK

Attention: Roger Crystal, M.D.  
CEO

Dear Dr. Crystal:

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

We also refer to the meeting between representatives of your firm and the FDA on May 24, 2012. The purpose of the meeting was to discuss your development plan for the above proposed drug product.

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) 796-1175.

Sincerely,

*{See appended electronic signature page}*

Lisa Basham, 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:  
MEMORANDUM OF MEETING MINUTES

**MEMORANDUM OF MEETING MINUTES**

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

**Meeting Date and Time:** May 24, 2012, 4 PM (EST)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room 1313  
Silver Spring, MD 20903

**Application Number:** PIND 114704  
**Product Name:** Naloxone Hydrochloride Nasal Spray  
**Indication:** (b) (4) opioid depression, including respiratory depression, (b) (4)

**Sponsor/Applicant Name:** Lightlake Therapeutics, Inc.  
**Meeting Chair:** Sharon Hertz, M.D.  
**Meeting Recorder:** Lisa Basham, M.S.

**FDA ATTENDEES**

Bob Rappaport, M.D. Director; Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, M.D. Deputy Division Director; DAAAP

Frank Pucino, Pharm.D, M.P.H. Clinical Team Leader, DAAAP

Dan Mellon, Ph.D. Supervisory Pharmacologist, DAAAP

Srikanth Nallani, Ph.D. Acting Team Leader, Clinical Pharmacology, Division of Clinical Pharmacology II (DCP2)

Neville Gibbs, M.D., M.P.H. Clinical Reviewer, DAAAP

Danae Christodoulou, Ph.D. CMC Lead, Office of New Drug Quality Assessment; Office of New Drug Quality Assessment (ONDQA)

Erica Pfeiler, Ph.D. Microbiologist; Office of Pharmaceutical Sciences; New Drug Microbiology Staff

Carlic Huynh, Ph.D. Preclinical Pharmacology Reviewer; DAAAP

Suresh Narahariseti, Ph.D. Clinical Pharmacology Reviewer, DCP2

Lisa Basham, M.S. Senior Regulatory Health Project Manager, DAAAP

**SPONSOR ATTENDEES**

Roger Crystal, M.D. CEO, Lightlake Therapeutics, Inc.

Mary Pendergast, J.D. Regulatory Consultant

Phil Skolnick, Ph.D., D.Sc. (hon.) Director; Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDCA); National Institute on Drug Abuse (NIDA); National Institutes of Health (NIH)

David McCann, Ph.D. Associate Director, DPMCDCA; NIDA; NIH

Nora Chiang, Ph.D. Chief; Pharmaceuticals Branch; DPMCDCA; NIH

## **BACKGROUND:**

The Sponsor submitted a Pre-IND meeting request on February 7, 2012, received February 21, 2012. The meeting was granted on March 8, 2012. The meeting package was submitted on March 29, 2012, received March 29, 2012. Preliminary responses to the questions contained in the meeting package were emailed to the Sponsor on May 19, 2012. On May 23, 2012, the Sponsor informed the Division that they wished to focus discussion during the meeting on our responses to Questions 1, 5, 6, and 8 (to obtain clarification), and our response to Question 9 (clinical Comments 1 and 2 only). For ease of reference, the questions are reproduced below in italicized text, followed by our preliminary responses, in bold text. Discussion during the meeting is labeled as such and written in normal text.

### Clinical

*Question 1: There is extensive previous human experience documenting the safety and efficacy of intravenous, intramuscular, and subcutaneous administration of naloxone HCl for the treatment of opioid overdose. In addition, naloxone is administered in oral and sublingual formulations as part of drug combinations for opioid dependent patients who require maintenance doses of opioids. There is also extensive documentation justifying and advocating the use of nasal administration of naloxone HCl as a standard of care for the treatment of opioid overdose. This standard of care using nasal naloxone is now formalized by many state and regional level public health organizations and is in practice throughout the US. As such, Lightlake anticipates that no new clinical studies other than the biopharmaceutics trial referenced below should be required to support a future NDA for its nasal naloxone products. Does FDA concur that no clinical trials other than the referenced biopharmaceutics trial are required for a future NDA for Lightlake's naloxone HCl nasal spray product configurations?*

### **FDA Response:**

**The need to conduct a clinical trial other than the proposed relative bioavailability study will depend on the results of this study. If the bioavailability of your product is the same or greater than a parenteral naloxone comparator administered at an approved labeled dose (i.e., 0.4 to 2 mg) and by an approved route of administration, then additional clinical efficacy studies will not be required. However, if the systemic exposure is less than the lowest approved dose, efficacy studies will be required. However, you will need to provide a rationale for why you would choose to pursue a product with lower systemic exposure and it is not entirely clear that efficacy studies of a lower systemic exposure would be feasible or ethical.**

**For your relative bioavailability study, we recommend that you evaluate at least two different nasal naloxone doses compared to parenteral injection of naloxone. Final dose selection must be based on the pharmacokinetic profiles observed in this study.**

**Depending on how much the intranasal and parenteral naloxone pharmacokinetic profiles differ, you may be required to provide additional safety data for an NDA submission. Further, the presence of novel excipients or container closures may require additional studies, and data regarding the usability of your product may be requested.**

## DISCUSSION:

The Sponsor opened the discussion with some general comments. They conveyed that they do not intend to (b) (4)

They noted that they may need to change the concentration for the Atomizer to reach a concentration and volume optimal for intranasal administration.

The Division clarified that, whether the Sponsor pursues repackaging or changes in concentration for nasal delivery, data are not currently available to make a regulatory decision regarding approval. Anecdotal evidence does not meet the standard for regulatory decision-making. Therefore, data must be collected in a systematic way, typically derived from adequate and well-controlled clinical investigations. A pharmacokinetic (PK) study comparing the area under the curve (AUC), maximum plasma concentration (C<sub>max</sub>), and time to maximum concentration (T<sub>max</sub>) obtained via intranasal administration to those of an approved drug administered via an approved route is necessary. The extent to which the PK profiles of the products must compare is difficult to predefine. Differences in C<sub>max</sub>, AUC, and/or T<sub>max</sub> will need to be qualitatively evaluated in terms of predicted efficacy.

The Division stated that it is not necessary to meet the strict definition of bioequivalence based on comparing the PK profile of the same dose of naloxone administered intranasally and by an approved route. It would be acceptable if a more concentrated naloxone product, or a higher dose of naloxone was needed to achieve the targeted PK characteristics by the intranasal route. In addition, this comparative bioavailability (BA) study would meet the bridging requirement for a 505(b)(2) NDA application. The Division suggested that the Sponsor consider conducting a dose-ranging study to provide the basis for the doses used in the comparative bioavailability (PK) study.

The Division noted that, for a product intended for single-administration, nonclinical studies may be waived if there are no novel excipients in the formulation and examination of the nares of subjects in the PK study reveals no local toxicity. Minor nasal passage irritation may be acceptable for a product of this nature and can be described in the label. Significant nasal tissue damage due to the formulation would be more problematic with respect to approvability and suggest the need for formulation changes.

The Sponsor inquired about the number of subjects needed for a comparative BA study. The Division responded that the number will depend on the variability of the response to intranasal delivery. The more variability observed, the more subjects will be needed. A literature review may provide some information, but the literature may be limited by a lack of sensitive analytical methods. Development of an assay that can measure naloxone concentrations down to 5 pg/mL would be helpful. The Sponsor stated that their current assay measures to 100 pg/mL. The Division emphasized that accurate ascertainment of absorption characteristics is very important.

A robust study, with narrow confidence intervals for the key PK parameters, would be important for achieving informative, reliable and interpretable data. A sensitive assay will add additional confidence for interpreting the comparative bioavailability data. The more robust the study and data are, the less likely there will be a need for additional data.

The Division noted that, if a concentration is chosen such that the intranasal PK parameter measurements (i.e., AUC and C<sub>max</sub>) exceed the PK measures from approved routes, this may not be an issue in itself (assuming the PK levels are not accompanied by adverse events) because the drug is not expected to be toxic at higher levels. In terms of volume, a reasonable starting approach is to identify the volume that the nose can realistically accommodate.

The Sponsor asked for confirmation that their comparative BA study should compare an approved naloxone product, dose and administration route to a range of intranasal naloxone doses. The Division agreed with this approach and noted that the approved label instructs practitioners to first administer 0.4 mg, but if this dose is not effective, consider administering a second dose. With this in mind, the Sponsor may wish to consider placing two dose units into each package. This provides an opportunity to administer a second dose if the first dose does not work, or to extend the effect, if needed.

The Sponsor expressed interest in

(b) (4)

### Nonclinical

*Question 2: Naloxone HCl injection has been marketed in the US and worldwide for over 40 years (naloxone HCl was first approved in 1971), and has well-established nonclinical and clinical safety profiles, including extensive previous human experience for nasal administration. FDA has approved four NDAs containing naloxone, and over four dozen ANDAs for naloxone as a single entity. The preclinical and clinical safety of naloxone was established in the original NDA for naloxone, and was re-established in the NDA for buprenorphine/naloxone NDAs approved in 2002 and 2010 (NDAs 020733 and 022410). Considering the above, Lightlake proposes that there are no new nonclinical safety issues associated with either the anticipated formulation of the nasal drug product, or the proposed clinical use of the nasal naloxone HCl drug product. Therefore it is reasonable to conclude that no additional nonclinical studies are necessary to support the future NDA. Does FDA concur that no GLP toxicity studies are required to support a future NDA for Lightlake's naloxone HCl nasal spray product configurations?*

#### **FDA Response:**

**No. Under typical circumstances, since naloxone is not approved for the intranasal route of administration, local tolerance studies in two species of adequate duration would be required to support your initial clinical studies and your NDA. However, since there is considerable clinical experience with intranasally administered naloxone and your formulation does not appear to contain novel excipients, in lieu**

of animal studies, you may assess the local tolerance by adequate clinical monitoring of local tissues.

We note that you are currently proposing a drug product specification for (b) (4) of NMT (b) (4)%. This exceeds the current ICH Q3B(R2) qualification threshold of NMT 1% and therefore, must be adequately justified for safety.

**Additional Nonclinical comments:**

1. As you have not yet finalized your drug product formulations, we remind you that any new or novel excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND. Refer to Guidance for Industry: *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>
2. 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)
3. Any impurity or degradation product that exceeds ICH thresholds may need to be adequately qualified for safety as per (ICHQ3A), ICHQ3B(R2)) 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.
  - c. We may decide to 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.

Refer to Guidance for Industry: *Q3A Impurities in New Drug Substances* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>, and *Guidance for Industry: Q3B (R2) Impurities in New Drug Products* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

4. Phenanthrene-derivative opioid drug products, including naloxone, may contain impurities containing an (b) (4), which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance must be reduced to reflect a maximal daily intake of NMT 1.5 mcg/day or adequate safety qualification must be provided. Adequate safety qualification for any potential genotoxic impurities identified via a structural alert for mutagenicity must be provided with the NDA submission and must include an in vitro bacterial reverse mutation assay (Ames assay) with the isolated impurity, tested up to the limit dose for the assay. Should this qualification produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model. We recommend that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and, if needed, to decrease the limit of these impurities.
5. 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 and Q3B qualification thresholds along with a 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.
6. The NDA submission must contain complete and definitive safety information on potential leachables and extractables from the drug container closure system. 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>

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. 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 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, refer to FDA Guidance documents *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> Additional leachable extractable conditions and considerations regarding thresholds of toxicological concern 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).**

DISCUSSION: No discussion necessary.

*Chemistry, Manufacturing, and Controls*

*Question 3: Lightlake will source the naloxone HCl drug substance from a vendor(s) that holds a current US Drug Master File (DMF). Lightlake proposes to perform confirmatory testing based solely on the current United States Pharmacopeia (USP) monograph for naloxone HCl for batches received for the manufacture of drug product. Does FDA agree with this proposal?*

**FDA Response:**

**No we do not agree. The USP monograph provides the minimal quality requirements for naloxone HCl.**

- 1. Establish drug substance acceptance specifications, harmonized to those of your supplier, and include impurities/degradants specifications as per ICH Q3A. In addition, limit impurities that contain structural alerts for mutagenicity to NMT 1.5 mcg total daily dose at the NDA stage.**
- 2. Provide batch analysis data in your NDA including CoAs from the supplier and acceptance testing using drug substance specifications established by Lightlake.**
- 3. Use drug substance acceptance specifications for retest of the drug substance, periodic confirmation of the supplier's CoA and as qualifying criteria for any potential future supplier(s) of the drug substance.**

DISCUSSION: No discussion necessary.

*Question 4: The proposed Chemistry, Manufacturing, and Controls development plan for the three naloxone nasal spray product configurations are presented in Section 10.3. Does FDA*

*have any comments on the design or the proposed development plan for the three naloxone HCl nasal spray drug product configurations?*

**FDA Response:**

**CMC:**

- 1. Include Letters of Authorization to the Drug Master Files for the container closure systems and packaging components for your nasal spray(s) and prefilled syringe.**
- 2. Clearly identify and describe the device(s) to be used, including the MAD (e.g., model type and number) and include critical quality attributes, e.g., droplet size distribution. Provide documentation, e.g., regulatory status and CDRH clearance for the device. Note that CDRH may be consulted to assess human factors and compatibility issues for the device.**
- 3. Provide complete characterization of the spray characteristics, e.g., particle size distribution, fraction of droplet size (b)(4) micron, spray pattern, dose delivery, priming information, etc. Refer to 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>**
- 4. Include additional stability time points for your pump delivery testing in your NDA, at release, 3, 6, 9, 12, 18 and 24 months.**
- 5. Provide a leachables/extractables evaluation of your container/closure system with the drug product in the NDA, with characterization and assay of any new impurities and degradants. With regards to 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 the PQRI leachables/extractables recommendations to the FDA 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).**

Refer to the non-clinical comments regarding the safety evaluation of your leachables/extractables.

**Microbiology:**

**Please add USP<62> (Tests for Specified Microorganisms) or equivalent methods to the microbial test methods for the detection of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in the drug product.**

DISCUSSION: No discussion necessary.

### Biopharmaceutics

*Question 5: Lightlake proposes to conduct a single biopharmaceutics clinical study in support of a future NDA for the naloxone HCl nasal spray. This trial will be an open-label, randomized, two-period, two-treatment, two-sequence, single dose, crossover study comparing the nasal spray to the intramuscular administration of naloxone HCl reference listed product in healthy volunteers. The objectives of the study are to evaluate the safety and pharmacokinetics of single nasal and intramuscular administrations of naloxone in healthy volunteers.*

*Subjects will be randomized 1:1 to receive a single nasal dose of 2 mg naloxone HCl (1 mg per nostril) or a single intramuscular dose of 2 mg naloxone HCl (RLD for 1 mg/mL naloxone HCl injection; International Medication Systems' ANDA 072076), and then will crossover to the other treatment (i.e., intramuscular or nasal dose, respectively) after a 7 day washout period. Safety will be assessed by reported adverse events (AEs), physical examination, vital signs, 12-lead electrocardiogram (ECG), hematology, serum chemistry, and urinalysis. The pharmacokinetics of naloxone will be assessed in each treatment period.*

*The study will compare, using the above design, the single patient use disposable (b) (4) Luer-Lock prefilled syringe and nasal atomizer kit (4 mg) to the intramuscular RLD, and will compare the single patient use metered-dose nasal spray (4 mg) to the intramuscular RLD. The study will not include the multi-patient use metered-dose nasal spray (12 mg) because the drug product formation and pump design is identical to the single patient use configuration, differing only in the vial contents.*

*Does FDA agree with this approach to assessing the biopharmaceutics of the nasal spray drug product configurations for supporting the NDA?*

#### **FDA Response:**

**You have proposed to evaluate the relative bioavailability of 2 mg intranasal (IN) naloxone compared to 2 mg intramuscular (IM) naloxone in healthy volunteers. The three proposed configurations of naloxone HCl nasal spray drug product will deliver a 2 mg dose (i.e., 1 mg per nostril), with the option for administration of a second 2 mg dose if needed (4 mg total).**

**We note that population-PK studies in the literature indicate that the relative bioavailability of 2 mg naloxone via the IN route is relatively poor in comparison to 2 mg administered via the IM route (Dowling et. al. *Ther Drug Monit.* 2008; 30(4): 490-6). Therefore, as you intend to use a 2 mg IM naloxone dose in the relative bioavailability study, you may need to consider increasing the dose of your proposed product to achieve systemic exposure comparable to the approved comparator product. In view of this, you may want to consider conducting a preliminary study to evaluate the exposure of naloxone by the IN route at multiple dose levels. For comparison of plasma levels and bioavailability of the IN doses, we recommend**

**including a parenteral naloxone treatment arm in the same study. Based on comparison of naloxone plasma concentrations following IN and parenteral administration, you may be able to determine an appropriate IN dose for the pivotal relative bioavailability study. You may also use published data with IN naloxone PK information to help select the dose. Additionally, this pilot study could serve as a pivotal relative bioavailability study provided the study design is adequate and the data are robust.**

**In order to obtain a reliable estimation of the PK parameters from the relative bioavailability study, we recommend that an adequate sample size be calculated. Further, it is recommended that you use the bioequivalence method to analyze the data.**

**You have proposed three configurations of naloxone HCl nasal spray drug product. In the proposed relative bioavailability study, you indicated that only the two single-patient use metered-dose nasal spray configurations will be tested, while the multi-patient use configuration will not be tested. The differences in the nasal spray configurations may result in different drug delivery and PK profiles. In view of this, all three configurations must be tested in the relative bioavailability study. If you think that the multi-patient use configuration will result in similar bioavailability as the other two configurations, you can request a biowaiver with an appropriate justification for Agency consideration.**

**You must use an adequately validated bioanalytical method to determine the plasma concentrations of both free (unconjugated) and total (conjugated plus unconjugated) naloxone. You should develop and validate an analytical method that is sensitive enough to detect and quantitate plasma levels of free and total naloxone. You must ensure that your bioanalytical method is accurate, precise, selective, sensitive, and reproducible. Refer to Guidance for Industry: “Bioanalytical Method Validation”**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>

**Use the final to-be-marketed product in the proposed studies. Otherwise, provide adequate bridging information or justification as to why the data can apply to your final to-be-marketed formulation.**

DISCUSSION: See discussion under Question 1.

### Regulatory

*Question 6: Lightlake anticipates that a future NDA filing for naloxone HCl nasal spray will be a 505(b)(2) submission. The application will be a 505(b)(2) application because it is a different route of administration than approved versions of naloxone HCl. The NDA for naloxone HCl nasal spray will reference Endo Pharms’ discontinued naloxone HCl injection (Narcan, NDA 016636). The RLD for 1 mg/mL naloxone HCl injection (International Medication Systems’ ANDA 072076) will be used in the proposed biopharmaceutics trial. Does FDA concur that the*

*NDA for naloxone HCl nasal spray would be a 505(b)(2) submission and that the above NDA would serve as the appropriate reference for safety and efficacy and the above ANDA as the appropriate RLD for the biopharmaceutics trial?*

**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, you may only rely upon the Agency’s finding of safety and effectiveness for one or more NDAs, not an ANDA, that contain the active drug moiety in the investigational drug product. Further, you must reference and provide patent certification for that NDA product.**

**Your proposal to rely on the Agency’s findings of safety and effectiveness for Narcan (NDA 16636) and, as Narcan is no longer available on the market, to use the generic naloxone product, ANDA 072076, as a comparator for your relative bioavailability (“bridging”) study is acceptable.**

DISCUSSION: See discussion under Question 1.

*Question 7: Lightlake is relying on the safety and efficacy assessments for Endo Pharms’ discontinued naloxone HCl injection (Narcan, NDA 016636) and is not pursuing any additional indications. As such, Lightlake plans to use the existing labeling for the Narcan product, revised to account for the change in the drug product [REDACTED] (b) (4) [REDACTED] the nasal route of administration, and any additional product specific changes. The labeling will be reformatted according to FDA’s most current 2006 labeling regulations (i.e., the labeling for the naloxone HCl injection product is currently based on outdated labeling regulations). Does FDA concur with this approach?*

**FDA Response:**

**In general, your approach to reformat the existing Narcan label, by taking into account the change in the route of administration, use of a specific drug delivery device, results of the relative bioavailability study, product specific changes, and labeling regulations may be acceptable. However adequacy of product labeling will be determined at the time of your NDA submission.**

DISCUSSION: No discussion necessary.

*Question 8: Lightlake is relying on the safety and efficacy assessments for Endo Pharms’ discontinued naloxone HCl injection (Narcan, NDA 016636) and is not pursuing any additional indications. As such, Lightlake proposes that the NDA not include any nonclinical study reports or literature references (CTD Module 4) and no nonclinical summaries (CTD Sections 2.61 through 2.67). Does FDA concur with this approach?*

**FDA Response:**

**No.** As Narcan was approved in 1971, your NDA submission should include a detailed discussion of any new nonclinical information in the published literature since approval and should specifically address how the information within the published 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.

DISCUSSION: See discussion under Question 1.

*Question 9: Lightlake is relying on the safety and efficacy assessments for Endo Pharms' discontinued naloxone HCl injection (Narcan, NDA 016636) and is not pursuing any additional indications. As such, Lightlake proposes that the NDA include one clinical study report on the bioavailability study proposed above and no other clinical study reports or literature references (CTD Module 5) and no clinical efficacy or safety summaries (CTD Sections 2.73 and 2.74), with the exception of the safety summary from the one proposed bioavailability study. Also, no integrated summary of efficacy (ISE) and no integrated summary of safety (ISS) are planned to be included. The clinical summary section 2.7.1 Biopharmaceutics and 2.7.2 Clinical Pharmacology will present the summary of the one proposed biopharmaceutics trial. Does FDA concur with this approach?*

**FDA Response:**

**No.** You will need to provide a separate Summary of Clinical Efficacy, Summary of Clinical Safety, Integrated Summary of Efficacy, and Integrated Summary of Safety per applicable regulations and guidance. In the Integrated Summaries of Efficacy and Safety, make sure that you provide a scientific rationale to link to previous findings of efficacy and safety for naloxone.

Provide a review of the literature related to the efficacy and safety of intranasal naloxone and submit all published literature cited in the Clinical Overview (Module 2.5) and Clinical Summary (Module 2.7) to Module 5.4 in accordance with ICH guideline M4E. Additionally, place the complete study report for your relative bioavailability study in Module 5.3.

Refer to the following guidance documents:

**Guidance for Industry: *Integrated Summary of Effectiveness and Safety: Location Within the Common Technical Document***

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

**Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – General Considerations***

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072362.pdf>

**Guidance for Industry: M4E: The CTD – Efficacy**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073290.pdf>

**Additional Comments:**

**Microbiology:**

**Should development of this product proceed to the NDA stage, be aware of the following information necessary for a microbiology review of an NDA of this type of drug product:**

1. For the presentations containing the (b) (4) benzalkonium chloride, conduct antimicrobial effectiveness testing using batches of the drug product containing (b) (4) levels at or below the lowest specified concentration. USP (b) (4) lists methods for antimicrobial effectiveness testing.
2. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources be examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. The test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

**Clinical:**

1. During the clinical development program, it will be important to have adequate clinical monitoring of local tissues (i.e., nasal passages) during the clinical trial(s), especially if your product contains novel excipients.
2. Since your product may be intended to be used by consumers, healthcare providers, family members and friends, it will be important to demonstrate that these end-users are able to administer your product appropriately. Therefore, a Label Comprehension Study and possibly a Human Factor Study may be required. Refer to the following guidance documents:

**Guidance for Industry: Label comprehension Studies for Nonprescription Drug Products**

[www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM143834.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM143834.pdf)

**Guidance for Industry: *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management***  
[www.fda.gov/.../DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm](http://www.fda.gov/.../DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm)

DISCUSSION (Clinical Comments 1 and 2, above): The Division explained that the product will require Instructions For Use (IFU). Furthermore, if use of the product is not straightforward, e.g., if assembly is required, a formal label comprehension study may be required. It was acknowledged that with some prescription products, dosing accuracy has been a concern. If that issue can be eliminated as much as possible (by not requiring priming or by using a single-dose device) this concern may be minimized. Additionally, the Sponsor should ensure consistent delivery of naloxone when the device is horizontal, as most patients are likely to be lying down when the drug is administered. All of these issues are covered in the guidance for nasal sprays listed under Question 4, CMC Comment 3.

ADDITIONAL DISCUSSION: The Sponsor asked whether the Division would be willing to review their proposed PK study protocol. The Division stated that the Sponsor should consider opening their IND with the protocol. This is preferable because all aspects of the proposal will be evaluated, including the device and excipients. If requested, the IND will likely receive Fast Track designation since the proposed product provides an advantage over existing products, treats a serious/life-threatening condition, and addresses an unmet medical need. As for NDA review, if the PK profile is very different between the intranasal and approved administration routes, an Advisory Committee meeting may be convened. The Division emphasized their commitment to work with the Sponsor to ensure that their IND is complete and reviewable. The Sponsor was encouraged to submit their IND electronically, if possible, as this approach facilitates the review process.

The Division stated that, if more than one device configuration is to be developed, then all configurations must be tested in the comparative BA study. The Sponsor stated that they will likely develop two configurations. The Division suggested that a single-dose configuration, that does not require priming, may be the preferred option, as most multi-dose configurations require priming. A single-dose configuration often has a single glass vial inside, eliminating the concerns regarding leachables or extractables from the glass vial. Two dosing units can be packaged together, one for each nostril, or one for the initial dose, and a second for follow-up administration, if needed.

The Sponsor summarized the discussion below.

**Key Discussion Points**

1. The Sponsor will develop a robust PK study that attempts to match the PK profile of an approved naloxone product administered at an approved dose and route.
2. Prior to conducting the comparative BA study, the Sponsor will first conduct a pilot dose-ranging study to inform dosing.
3. The Sponsor will submit the PK protocols to the Division for review.

4. The Sponsor will request Fast Track designation.
5. The PK parameters will focus on AUC, Cmax, and Tmax. Use of the bioequivalence method is recommended to generate robust PK data to compare the bioavailability of the formulation to be developed to an approved parenteral route of administration.
6. The Sponsor will look for models of IFU that make sense for this product.
7. The CMC requirements will be standard and per the Agency's Nasal Spray guidance document.
8. Non-Clinical requirements will be limited to safety justification for the container closure, any novel excipients, and drug substance impurities and drug product degradants, assuming adequate clinical nasal examination of subjects for local irritation does not suggest a safety concern for the formulation. If anything beyond minor local tissue irritation is observed, drug product formulation changes should be considered that may require additional nonclinical studies.
9. The Sponsor should review the published clinical and nonclinical literature for studies conducted after the Narcan approval date that will inform their program and product labeling. The Sponsor is not expected to, and should not, submit study reports for published literature references.

Post-meeting comments for the bioanalytical assay from Office of Scientific Investigation:

Note that all the items in the Guidance for Industry: "*Bioanalytical Method Validation*," as referred to in Question 5, are important. You should comply with this guidance and take notice of the following:

- Considering the route of administration, the assay should be of sufficient sensitivity to perform adequate PK evaluation.
- Maintain adequate record keeping to allow for complete reconstruction of all study-related events (clinical and bioanalytical including method validation).
- Select proper quality control (QC) and calibration samples so that they cover the range of expected PK concentrations. Modify if necessary after analysis of a few subjects.
- Provide a demonstration of accuracy and precision for the method and also from QCs and calibrators made from separate stocks.
- Use identical anticoagulant for the QCs and calibrators between method validation and study sample analysis. Cross validation is necessary if alternate matrix is used during method validation.
- Demonstrate stabilities during method validation (bench top, freeze-thaw, long term, processed samples). Refer to Guidance for Industry: *Bioanalytical Method Validation* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>

- Note the minimum requirements for retention of BA and BE samples. Refer to Guidance for Industry: *Handling and Retention of BA and BE Testing Samples*  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>

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/s/  
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LISA E BASHAM  
06/18/2012