

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208411Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

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

---

NDA # 208411  
Product Name: NARCAN (naloxone hydrochloride) nasal spray

---

PMR/PMC Description: PMR #2990-1

Establish reliability requirements for the combination product Narcan Nasal Spray (naloxone hydrochloride), and complete testing which verifies the combination product reliability.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	02/2016
	Study/Trial Completion:	09/2016
	Final Report Submission:	11/2016
	Other: N/A	MM/DD/YYYY

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

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

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

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

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

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

The study will be a bench-top engineering study. It will examine the reliability of the combination product after simulated exposure to storage, shipping, and in-use conditions.

Required

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

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☒ Other (provide explanation)  
Device reliability testing studies
- 

Agreed upon:

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

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

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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



---

**PMR/PMC Development Coordinator:**

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

---

(signature line for BLAs)

## PMR/PMC Development Template

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

---

NDA # 208411  
Product Name: NARCAN (naloxone hydrochloride) nasal spray

---

PMR/PMC Description: PMR #2990-2

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

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>02/2016</u>
	Study/Trial Completion:	<u>N/A</u>
	Interim Report:	<u>01/2017</u>
	Final Report Submission:	<u>01/2018</u>

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

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

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

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

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

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

This is a requirement to monitor and report any instances of failure of the combination product to activate or failure of the combination product to deliver the full labeled dose.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

- 
- ☐ Other
- 

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

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

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

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

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

---

**PMR/PMC Development Coordinator:**

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

---

(signature line for BLAs)

## PMR/PMC Development Template: Product Quality (CMC)

NDA # NDA 208411  
Product Name: NARCAN nasal spray

PMC #2990-3

PMC #2990-3  
Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	02/2016
	Interim Report Submission:	01/2017
	Final Report Submission:	11/2017
	Other:	MM/DD/YYYY

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

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☒ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

Potential leachables from the container closure system have not been quantified to date and prior clinical experience does not fully address their safety. There is a concern that due to the nature of the materials in the container closure, some of the impurities may result in the potential for adverse effects. However, the rubber stopper in the container closure system has been used in other FDA-approved drug products. Given the clinical experience with this (b) (4) plunger, and based on preliminary extractables data suggesting no significant concerns, this study was deemed acceptable as a post-marketing commitment.

2. Describe the particular review issue and the goal of the study.

Although the rubber stopper that is part of the container closure system has been used in several FDA-approved drug products, the leachable profile of the NARCAN nasal spray has not been fully characterized. It is possible that chemicals from the plunger can leach into the drug solution over time. This study will be completed to characterize the potential leachables over stability and assess the safety of the container closure based on current practices.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☒ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

The study is a leachable study over the course of stability to more fully characterize the container closure system.

4. To be completed by ONDQA/OBP Manager:

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

---

**PMR/PMC Development Coordinator:**

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

---

(signature line for BLAs only)

## PMC Development Template: Product Quality (CMC)

NDA #	NDA 208411	
Product Name:	NARCAN nasal spray	
PMC #2990-4	PMC #2990-4	
Description:	Conduct a long- term stability evaluation placing at least three (3) manufactured lots of NARCAN Nasal Spray, 40 mg/mL, on long- term stability evaluation at the following temperatures:	
	a. 2 to 8°C	
	b. 40°C/75% RH - to extend the time points out to 24 months	
PMC Schedule Milestones:	Final Protocol Submission:	02/2016
	Interim Report Submission (12 months):	06/2017
	Final Report Submission (24 months):	06/2018

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

- ☒ Need for drug (unmet need/life-threatening condition)
- ☒ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

Since this product will be stored in Police cars and ambulances through the country, the stability of the product at temperatures ranging from 4C to 40C is needed. Some limited data is provided in the NDA but given the importance of the product for life-threatening conditions, a more thorough study is deferred to post-approval.

2. Describe the particular review issue and the goal of the study.

The Stability study will provide data to demonstrate that the product will remain stable, without precipitation or degradation, under a wide temperature range.

3. What type of study is agreed upon (describe and check type below)?



Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☒ Assay
- ☐ Sterility
- ☐ Potency
- ☒ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☒ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

The Sponsor has agreed to provide data from a 24 month study, to determine potency, dose delivery and potential degradation of the product when stored under vigorous conditions of low and high temperatures.

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

---

**PMR/PMC Development Coordinator:**

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

---

(signature line for BLAs only)

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

/s/  
-----

DIANA L WALKER  
11/18/2015

JUDITH A RACOOSIN  
11/18/2015

## 505(b)(2) ASSESSMENT

Application Information		
NDA # 208411	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Narcan Nasal Spray Established/Proper Name: naloxone hydrochloride nasal spray Dosage Form: liquid, intranasal spray Strengths: 4 mg per unit-dose sprayer (100 mcL)		
Applicant: Adapt Pharma Operations Limited		
Date of Receipt: July 20, 2015		
PDUFA Goal Date: January 20, 2016		Action Goal Date (if different): November 18, 2015
RPM: Diana Walker		
Proposed Indication: Treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.		

### GENERAL INFORMATION

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

YES ☐ NO ☒

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

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

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Narcan (naloxone hydrochloride; NDA 016636)	The Applicant owns this NDA and is cross-referencing the Agency's previous findings of safety and effectiveness for Narcan
Published Literature	<i>Pediatric assessment:</i> Narcan is approved for the full pediatric age range; however, labeling recommends weight-based dosing. The proposed product is a fixed dose. Therefore, the Applicant was required to submit literature to support the safety and effectiveness of this fixed dose of naloxone for the entire pediatric age range.

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

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature<sup>1</sup>.

[See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The applicant bridged to the findings for Narcan (NDA 016636), which the Applicant owns, by conducting a relative bioavailability study (study Naloxone-Ph1a-002) comparing the proposed final to-be-marketed product to an ANDA product of Narcan (NDA 016636) because Narcan was discontinued for marketing purposes. The ANDA product (Naloxone hydrochloride for IM injection) that was used in the relative bioavailability study was sourced from a commercial supplier and manufactured by Hospira Inc., Lake Forest, IL.

Literature was required as part of the pediatric assessment to support pediatric labeling. These studies either list Narcan or the generic name, naloxone, and the Applicant established a bridge to their Narcan NDA by conducting a relative bioavailability study.

**RELIANCE ON PUBLISHED LITERATURE**

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

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

YES ☒ NO ☐

*If “NO,” proceed to question #5.*

**The literature is required for the pediatric assessment to support pediatric labeling**

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

YES ☒ NO ☐

*If “NO,” proceed to question #5.*

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

**Narcan**

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

YES ☐ NO ☐

**The Applicant owns the Narcan NDA (NDA 16636)**

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

## RELIANCE ON LISTED DRUG(S)

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

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

YES ☐ NO ☒

*If "NO," proceed to question #10.*

**The Applicant is not relying on the Agency's finding of safety and efficacy for Narcan (NDA 16636), instead, they are cross-referencing this NDA, which they own, to support the Narcan nasal spray NDA.**

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

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

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☐

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

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

- b) Approved by the DESI process?

YES ☐ NO ☐

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

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

c) Described in a final OTC drug monograph?

YES ☐ NO ☐

If “YES”, please list which drug(s).

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

d) Discontinued from marketing?

YES ☐ NO ☐

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

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

**The Applicant is cross-referencing their NDA for Narcan, and the current NDA for Narcan nasal spray represents a change in dosage form from solution for injection to liquid nasal spray and change in route of administration from injection to intranasal, as compared to Narcan.**

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

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

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

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity,*

disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

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

YES ☐ NO ☒

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

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

YES ☐ NO ☐

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

N/A ☐ YES ☐ NO ☐

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

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

Pharmaceutical equivalent(s):

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

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

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

YES ☒ NO ☐

If "**NO**", proceed to question #12.

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

YES ☒ NO ☒

**One of the alternatives is approved for the same indication and one of the alternatives is approved for a similar indication**



(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
N/A ☒ YES ☐ NO ☐

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

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

Pharmaceutical alternative(s): Narcan (NDA 016636): approved for a similar indication  
Approved generics to Narcan are listed in the Orange Book

Evzio (NDA 205787): approved for the same indication

#### PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

No patents listed ☒ proceed to question #14

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

YES ☐ NO ☐

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

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

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

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

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

Patent number(s):

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

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

- (a) Patent number(s):

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

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

Date(s):

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

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

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

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

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

/s/  
-----

DIANA L WALKER  
11/18/2015

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

**PATIENT LABELING REVIEW**

Date: November 12, 2015

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

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

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

From: Nathan Caulk, MS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

L. Sheneé Toombs, Pharm.D.  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI),  
Instructions for Use (IFU), and Quick Start Guide (QSG)

Drug Name (established name): NARCAN (naloxone hydrochloride)

Dosage Form and Route: nasal spray

Application Type/Number: NDA 208411

Applicant: Adapt Pharma Operations Limited

## 1 INTRODUCTION

On July 20, 2015, Adapt Pharma Operations Limited submitted for the Agency's review the final portion of a rolling submission for 505(b)(2) New Drug Application (NDA) 208411 for NARCAN (naloxone hydrochloride) nasal spray. The purpose of this submission is to propose an intranasal formulation for NARCAN (naloxone hydrochloride) nasal spray. The proposed indication for NARCAN (naloxone hydrochloride) nasal spray is for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. NARCAN (naloxone hydrochloride) nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on August 5, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), Instructions for Use (IFU), and Quick Start Guide (QSG) for NARCAN (naloxone hydrochloride) nasal spray.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and separate DMEPA reviews of the IFU and QSG were completed on September 3, 2015 and October 13, 2015.

## 2 MATERIAL REVIEWED

- Draft NARCAN (naloxone hydrochloride) nasal spray PPI, IFU, and QSG received on July 20, 2015, revised IFU and QSG received September 23, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 2, 2015.
- Draft NARCAN (naloxone hydrochloride) nasal spray Prescribing Information (PI) received on July 20, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 2, 2015 and November 5, 2015.
- Approved EVZIO (naloxone hydrochloride injection) NDA (b)(4) comparator labeling dated April 3, 2014.

## 3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

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

- simplified wording and clarified concepts where possible
- ensured that the PPI, IFU, and QSG are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI, IFU, and QSG are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI, IFU, and QSG met the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI, IFU, and QSG are consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI, IFU, and QSG are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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

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

/s/  
-----

NATHAN P CAULK  
11/12/2015

LATOYA S TOOMBS  
11/12/2015

BARBARA A FULLER  
11/12/2015

LASHAWN M GRIFFITHS  
11/12/2015



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

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

*Memorandum*

Date: November 6, 2015

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

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

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

Subject: NDA 208411  
OPDP labeling comments for NARCAN (naloxone hydrochloride) nasal  
spray  
Labeling Review

---

OPDP has reviewed the proposed package insert (PI), proposed Patient Information (PPI), Instructions for Use (IFU) and Quick Start Guide (QSG) for NARCAN (naloxone hydrochloride) nasal spray (Narcan) that was submitted for consult on August 5, 2015. Comments on the proposed PI are based on the version sent via email from Diana Walker (RPM) on November 2, 2015 entitled "Draft Package Insert 30Oct2015.docx" and comments on the carton and container labeling are based on the draft carton/container labeling submitted October 8, 2015.

Comments regarding the PI are provided on the marked version below.

**Carton and Container Labeling Comments**

OPDP notes that the information contained under the header "OPEN HERE FOR QUICK GUIDE" on the carton labeling is the same as the information included in the Quick Start Guide document. OPDP comments regarding the Quick Start Guide will be provided under a collaborative review with DMPP.

We have no further comments on the draft carton/container labeling at this time.

Please note that comments on the PPI, IFU and QSG will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for the opportunity to comment.

If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or [latoya.toombs@fda.hhs.gov](mailto:latoya.toombs@fda.hhs.gov).

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

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

/s/  
-----

LATOYA S TOOMBS  
11/06/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

**MEMORANDUM**

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** November 5, 2015

**From:** Ryan McGowan  
Biomedical Engineer, General Hospital Devices Branch  
CDRH/ODE/DAGRID/GHDB

**To:** Diana Walker  
Regulatory Health Project Manager  
CDER/OND/ODEII/DAAAP

**Subject:** ICC1500397; NDA208411; CDRH/ODE Review of Combination Product Device Design

**Recommendation:** Approvable for device constituent part design considerations  
(2) Post-market Requirement/Commitment for device reliability

---

**I. Review Summary and Final Recommendation**

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the of the device constituent parts of the subject combination product. After examination of the original new drug application (NDA), cross-referenced drug master files (DMF), and responses to information requests, the consulting reviewer has determined that the device constituent parts of the combination product have been designed appropriately for the product's intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture.

The reviewer was not able to locate information which assures that the combination product is free from unacceptable risk with respect to the potential for under-dose or failure-to-dose events. Specifically, the sponsor has not demonstrated that a population of manufactured product is able to activate reliability after conditioning to applicable environmental or physical effects.

The consulting reviewer discussed the lack of reliability information available within the submission record with CDER/OND/ODEII/DAAAP within a September 23, 2015 mid-cycle meeting and an October 22, 2015 wrap-up meeting. The review division agreed with the consulting reviewer's assessment that additional information is needed regarding combination product reliability, however given the benefits of the product; the review division determined that this information could be requested within a post-market commitment or post-market requirement. Please see the final section of this review memorandum for recommended post-market commitment/requirement language regarding combination product reliability.

Therefore, the consulting review finds this submission to be approvable for device constituent part design considerations and requests commitment from the sponsor to engage in post-market activities to verify combination product reliability.

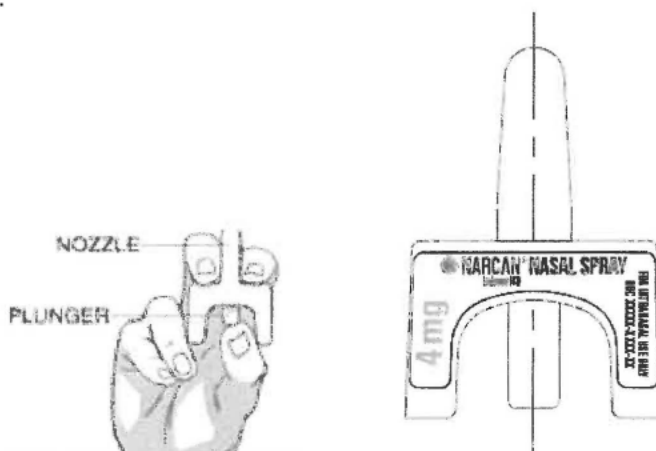
## II. Background and System Description

Adapt Pharma Ltd has submitted NDA 208411 for Agency review of NARCAN (naloxone hydrochloride) NASAL SPRAY, (0.4 mg/spray). This is a 505(b)(2) application under the Federal Food, Drug & Cosmetic Act (FDCA).

NARCAN NASAL SPRAY is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Naloxone HCl Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present.

NARCAN NASAL SPRAY consists of a formulated drug product filled into a unit-dose vial which is stoppered and placed within a Unit-dose Delivery Device produced by (b) (4). This unit-dose device is then placed into a single blister pack. The container closure-spray device is a single-entity combination (drug/device) product.

The proposed dosing of the Naloxone HCl Nasal Spray consists of 1 spray in one nostril (0.4 mg/spray) for a total dose of 4 mg, to be repeated if a second dose is available and insufficient response is observed.



The sprayer system is manufactured by a third part sponsor named (b) (4). This third party sponsor has provided a number of non-clinical resources to support approval of NDA 208411. The specific (b) (4) sprayer devices used within the subject NDA is stated as also used within other nasal and sublingual spray products in the U.S. (b) (4)

## III. Submission Content Reviewed by CDRH/ODE

The CDRH/ODE reviewer performed an evaluation of the design of the device constituent parts of the combination product. This evaluation covered the intended design and design control information for the subject device constituent part.

This review covered the following review content:

- Inspection of sponsor's design input activities
- Inspection of sponsor's design verification activities
- Confirmation of standards conformance, where relied upon
- Inspection of test methods and results of bench top testing completed
- Inspection of stability testing completed on the device constituent part

- Inspection of master file information, where appropriate and available

This review covered the following review materials:

- NDA208411 Electronic Document Record: 0001 (2) 5/29/15
- NDA208411 Electronic Document Record: 0010 (11) 9/23/15

MAF/DMF Note: Master files cited and cross-referenced by the sponsor were reviewed only where necessary, defined as the NDA having insufficient evidence to support use of the device sub-component. The sponsor is expected to submit sufficient information to demonstrate function and safety of the device constituent parts in their final finished form within the NDA submission materials.

This review **did not cover** the following review content:

- Review of drug product
- Review of primary container closure-drug product interaction or biocompatibility/toxicology
- Final assessments of usability/human factors of the combination product
- Manufacturing of the drug product
- Manufacturing of the device constituent part of the combination product

Notes on Review Jurisdiction:

Container Closure: Evaluation of the suitability of the primary container closure materials (e.g. stopper, glass container, caps/sealing disks and associated coatings and treatments) was not reviewed by the CDRH/ODE consultant and is deferred to appropriate CDER non-clinical reviewers.

Human Factors: Evaluation of the usability of the final finished combination product is deferred to the appropriate reviewers within CDER/OSE/DMEPA

Device Manufacturing and Compliance: According to an email exchange with Juandria Williams on 8/24/2015, review of device manufacturing and compliance, in particular with combination product part 4 regulations, is being conducted collaboratively between CDER/OPQ/OPF/DIA/IABII and CDRH/OC.

Review of Combination Product Performance: According to discussions with Venkateswara Pavuluri, review of all essential combination product performance attributes will be conducted by CDER/OPQ/ONDP/Div II/Branch IV. Reviewers within the group will apply the requirements described within the July 2002 FDA guidance titled "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation.

#### **IV. Device Constituent Part Description**

NARCAN NASAL SPRAY is comprised of an assembly of parts. These components include:

1. Glass vial with stopper
2. Unit-dose Actuator
3. Vial Holder

#### Vial and Stopper

NARCAN NASAL SPRAY is packaged in a USP Type I (b) (4) glass vial supplied by either (b) (4). Vials are sealed with a black (b) (4) rubber plunger manufactured by (b) (4). This comprises the primary container closure system. The secondary packaging of nasal drug delivery system is comprised of the (b) (4) Unitdose nasal spray actuator device which encloses this stoppered vial.



#### Unit Dose Actuator

The (b) (4) Unitdose nasal spray actuator device assembly encloses the (b) (4) glass vial sealed with a (b) (4) stopper. The vial and stopper remain sealed until the system is activated for drug delivery. The actuator contains an internal cannula and fluid path which puncture the vial stopper during activation, forcing contents into the nasal cavity.



#### Vial Holder

The vial holder component receives and retains the vial and stopper. This component also completes the primary closure when it is seated into the actuator component.

A schematic of the fully assembled system (vial holder and actuator enclosing the vial and stopper) is included below:

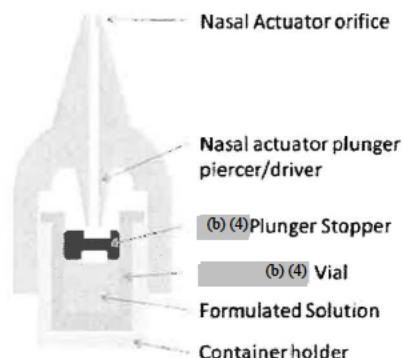


Figure 3 - Assembled Device

#### V. Review of Device Constituent Part Design

The consultant performed a review of device requirements and specifications. This review, in combination with accepted performance aspects of delivery systems known to CDRH, yielded the following list of items for inspection and evaluation within this memorandum.

1. Adequate combination product design inputs
2. Adequate combination product verification activities, including:
  - a. Compatibility, connection, sterility, and biocompatibility of device components
  - b. Functionality and accuracy of device components
  - c. Stability of device components
3. Evaluation of Combination Product Risks

#### Combination Product Design Inputs

Section 3.2.P.7 of the original submission contains a document titled "Container Closure System". This document provided a number of requirements and specifications for the primary container device components. A summary of these design inputs are provided below:

Component	Requirements/Specifications
Vial and Stopper	Visual inspection/assessment (b) (4) material characteristics Colorant characteristics Dimensional characteristics Meets (b) (4) limits per USP
Assembled Spray Product	Visual inspection/assessment (b) (4) material characteristics Colorant characteristics



	<p>Dimensional characteristics</p> <p>Meets (b) (4) limits per USP</p> <p>Shot Weight (b) (4)</p> <p>(b) (4)</p>
--	--

The above listing of device constituent part requirements were not considered sufficient to describe the combination product as they did not specify system requirement of the final finished and assembled device (instead they represented incoming product/supplier confirmation activities). After consultation with Julio Pinto (CMC team lead in CDER/DAAAP), the consulting reviewer was advised to consult with the pharmaceutical batch record/associated stability information for the product.

Within section 3.2.P.8 and 3.2.P.5 were consulted. These sections contained batch analysis reports from newly manufactured and aged product. The following is a summary of the device-relevant product requirements information located within these documents:

Attribute	Requirement
Visual Inspection of Container Closure System – Complete (b) (4) Delivery Device	Clear glass vial with black plunger. No visual defects.
Nasal Pump Delivery	Individual actuations of 10 within: (b) (4) Mean of 10 sprays: (b) (4)
Dose Content Uniformity- % dose emitted	No greater than one actuation of 10 actuations outside 85-115% of label claim;  None of 10 actuations less than (b) (4)% or greater than (b) (4)% of label claim; % mean of 10 actuations: (b) (4)% of label claim
Spray Pattern (b) (4)	D D D D Span: (b) (4) % (b) (4)

The above referenced requirements were evaluated by the consulting reviewer and considered to be acceptable with the exception of dose content uniformity, which appeared to allow for a batch to be released with relatively wide specifications. The consulting reviewer communicated this concern to the

CMC reviewer who then contacted the lead clinical reviewer. The consulting reviewer defers acceptability of the specification to the clinical and CMC reviewers.

#### Combination Product Verification Activities

A majority of the combination product verification activities are considered as performed and recorded under batch manufacturing validation records and stability assessments associated with the NDA. These include each of the attributes specified within the prior section.

All essential combination product performance attributes will be conducted by CDER/OPQ/ONDP/Div II/Branch IV. Reviewers within the group will apply the requirements described within the July 2002 FDA guidance titled "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation. Therefore, review of these verification studies is deferred and this memorandum will not contain evaluation of verification activities either after initial manufacturer or after stability.

To support biocompatibility of tissue-contacting components (outside of the container closure), the sponsor has provided reference to DMF (b) (4) submitted by (b) (4). This master file was found to contain reference to each material forming the tissue contacting components of the system along with a record of testing completed to assure safety of those materials. The table below contains details on the testing completed:

Material of Interest	Testing Completed
Unit-Dose (b) (4)	USP 661 – Containers: Physiochemical Tests – Plastics
(b) (4)	USP 87 Biological Reactivity, In Vitro
	USP 88 Biological Reactivity, In Vivo (b) (4)
Cannula	In conformance with (b) (4) 21.CFR178.3910

Each of the reports associated with the test summary shown above were inspected and found to be acceptable. For purposes of the limited duration and intact skin contacting portions of the system (nasal airway) the reviewer finds these tests equivalent in intent and purpose to the ISC (b) (4) suite of tests required for device constituent parts of combination products. Verification of biocompatibility is considered acceptable.

#### Evaluation of Combination Product Risks

The consulting reviewer was able to locate a discussion of combination product risks within the original submission within the 3.2.P.7 section.

The device risk analysis contained 8 risk items for the system. Most of these were related to use difficulties or to dimensional/physical issues with the spray device. Each failure mode was evaluated for occurrence and severity. Three risks were originally nominated as unacceptable "patient loses user guide", "does not insert into nostril", and "does not spray (due to mis-use)". Each of these risks, along with the remainder of the risks not considered as unacceptable, were then linked to corresponding verification activities intended to demonstrate that the risk had been controlled.

The sponsor also provided a high level "harms assessment" within 3.2.P.7, which included a more comprehensive assessment of the risks to the patient from the product. This harms analysis is focused on the potential harms and causes of drug over-dose and under-dose.

After consideration of the potential harms the device could cause, the reviewer has determined that the most likely and most severe event would be an under-dose or complete delivery failure as it may result in death due to non-reversal of respiratory depression. The sponsor also considers this to be a significant issue and has identified the following within their harms analysis:

Ref.#	Harm	Severity Rating	Occurrence	Overall Rating	Comments
01	Single "No dose" delivered by device	Critical	Low	Unacceptable requires mitigation	Potential life-critical administration: even at (b) (4) defect level assumed to high: requires to be very low
02	Multiple "No dose" delivered by device	Critical	Negligible	Acceptable	Second device failing at (b) (4) rate would be (b) (4) - (b) (4)
03	Single Low dose delivered by device	Important	Very Low	Acceptable	administration of second dose within 60-90 minutes more likely: instructed to seek emergency medical help right away
10	Partial insertion into nasal cavity	Important	Low	Acceptable	incomplete insertion giving incomplete dose would result in lower plasma levels and shorter duration: instructed to seek emergency medical help right away
11	Non insertion into nasal cavity	Critical	Low	Unacceptable requires mitigation	based on 5/63 subjects untrained inserting into mouth or into nostril and not spraying
17	Degraded drug	Negligible	Very Low	Acceptable	Not injected: based on stability data and qualification of impurities

Within the original submission, the sponsor did not clearly provide mitigations to the "unacceptable" harms/risks noted within the table above. The sponsor was requested to provide information concerning stated mitigations within an IR issued on 9/9/2015. On September 23, 2015 the sponsor provided a response to the information request. Within their response, they provided the following information:

- Two harms required significant mitigation actions these were Risk 01 Single No Dose Delivered by device and Risk 11 Non Insertion into Nasal cavity
- For Risk 01 - No Dose, the sponsor considered the following:

#### Causes

- o Device Components – Vial, Plunger Stopper, Vial Holder and Nasal Actuator
- o Device Filling and Assembly – conducted at (b) (4), including aspects of formulation process
- o Patient Transportation before Use
- o Patient Use
- o Patient Disposal

#### Controls

- o Component dimensional controls
- o Component assembly process

- In process and batch sample controls
- For Risk 11 - Non Insertion into Nasal cavity, the sponsor considered the following:

#### Causes

- Naïve user
- Improperly trained user

#### Controls

- Human factors testing

The reviewer evaluated the response summarized above and considered that for the “under-dose” and “no dose” risk, the sponsor had not provided sufficient information to demonstrate that the product achieved the intended dose after pre-conditioning to expected effects such as storage, aging, vibration, thermal changes, etc. For the sponsor’s response to Risk 11, the consulting reviewer defers review of usability issues to the CDER/OSE/DMEPA reviewer.

The reviewer identified the following device failure modes associated with under-dose and non-delivery hazards. Each risk is accompanied by mitigations that could be located within the submission.

Hazard	Sponsor Evidence to Control Hazard
User unable to activate device due to use-failures	Human factors summative validation
Failure to activate the device due to component fitment defect, finishing defect, or dimensional defect	No stated controls (would be completed as part of reliability assessment)
Failure to activate due to occluded fluid path	No stated controls (would be completed as part of reliability assessment)
Failure to activate due to bent cannula	No known controls other than “Cannula design improvement” as stated within Device Risk Analysis
Failure to activate due to activation orientation	No stated controls (would be completed as part of reliability assessment)
Spray pattern unacceptable per design	Batch analysis testing and adherence to Agency standard
Spray pattern unacceptable after aging	Stability assessments
Spray pattern unacceptable after aging in worst case orientation	Stability assessments
Drug degradation due to container	Compatibility monograph assessments
Drug degradation due to light	Light exposure monograph assessments
Failure to fill container during manufacturing	Fill controls and QC checks
Failure to fill container with correct drug substance	Deferred to CDER
Failure to activate due to shipping/vibration	No stated controls (would be completed as part of reliability assessment)
Failure to activate due to drop/mishandling	No stated controls (would be completed as part of reliability assessment)
Device leakage	Batch analysis testing and adherence to Agency standard shows total dose delivered

The sponsor has not demonstrated complete control of all risk nominated by the consulting reviewer which could lead to an under-dose or total delivery failure. Each of the hazards named above which are uncontrolled relate to either preconditioning of the device prior to use (shipping, orientation) or potential defects which may go unnoticed by assessment of the limited number of products challenged



under batch assessment (n = 20). Therefore the reviewer considers that these hazards should be assessed by a reliability study.

The sponsor was requested to provide information concerning combination product reliability within an IR issued on 9/9/2015. On September 23, 2015 the sponsor provided a response to the information request. Within their response, the sponsor offered a statistical approach to determining reliability of the system through an assessment of "shot volume", meaning the volume of medication dispensed. The figure below shows the distribution of shot volume across 25 devices tested with water. Based on relatively tight control of the shot volume, the sponsor argues that it is statistically improbable that a single device would offer a dose outside of the prescribed dose range.



While the consulting reviewer agrees that the data shown do demonstrate a high degree of control over shot volume, the sponsor's argument for this metric as a surrogate for product reliability is flawed in several ways:

- The testing was not completed on product which represents the final-finished drug product
- The testing was completed only with 25 samples and is not representative of a large-population reliability test
- The testing was not conducted on product that had been subjected to clinically relevant conditions such as age, temperature, vibration and the units were not activated in a worst case orientation.

The sponsor has not provided adequate information to assess the reliability of the combination product in terms of likelihood of under-dose and failure to dose. As such, the reviewer considers that additional information is required to characterize reliability of the combination product. The reviewer briefed CDER/OND/ODEII/DAAAP on this opinion within a September 24, 2015 mid-cycle meeting and October 22, 2015 wrap-up meeting. The review division agreed with the consulting reviewer's assessment that additional information is needed regarding combination product reliability, however given the benefits of the product the review division determined that this information could be requested within a post-market commitment or post-market requirement. Please see the review conclusion and post-market commit/requirement sections of this memorandum for additional detail.

#### **VI. Review Conclusion**

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the of the device constituent

parts of the subject combination product. After examination of the original new drug application (NDA), cross-referenced drug master files (DMF), and responses to information requests, the consulting reviewer has determined that the device constituent parts of the combination product have been designed appropriately for the product's intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture.

The reviewer was not able to locate information which assures that the combination product is free from unacceptable risk with respect to the potential for under-dose or failure-to-dose events. Specifically, the sponsor has not demonstrated that a population of manufactured product is able to activate reliability after conditioning to applicable environmental or physical effects.

The consulting reviewer discussed the lack of reliability information available within the review record with CDER/OND/ODEII/DAAAP within a September 23, 2015 mid-cycle meeting and October 22, 2015 wrap-up meeting. The review division agreed with the consulting reviewer's assessment that additional information is needed regarding combination product reliability, however given the benefits of the product; the review division determined that this information could be requested within a post-market commitment or post-market requirement. Please see the final section of this review memorandum for recommended post-market commitment/requirement language regarding combination product reliability.


## **VII. Post-Market Requirement/Commitment**

The consulting reviewer proposed the following draft language for a post-market commitments or requirements related to combination product reliability.

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:
  - 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.
  - Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
  - 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
- 2. Establish a post-market monitoring program for detection and evaluation of under-dose and failure-to-dose events, regardless of cause, and provide periodic reports to the Agency which contain descriptions of each reported event along with results of root-cause and contributing-cause analyses.

**VIII. Concurrence Table**

Concurring Party	Signature
Consultant	(b) (4)
Team Lead	
Branch Chief	 Richard C. Chapman -S 2015.11.05 16:01:33 -05'00'

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

/s/  
-----

MARY GRACE LUBAO  
12/01/2015



**MEMORANDUM**

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

---

DATE: October 30, 2015, 2015

TO: Sharon Hertz, M.D.  
Director  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Office of Drug Evaluation II  
Office of New Drugs

FROM: Arindam Dasgupta, Ph.D.  
Lead Pharmacologist  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

Yiyue Zhang, Ph.D.  
Visiting Associate  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

Melkamu Getie-Kehtie, Ph.D., R.Ph.  
Staff Fellow  
Division of Generic Drug Bioequivalence Evaluation (DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.  
Director  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Establishment Inspection Report covering NDA 208411,  
Naloxone hydrochloride nasal spray, sponsored by Adapt  
Pharma Limited, San Diego, CA

**Summary:**

At the request of the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion and arranged an inspection of the clinical portion of the following pharmacokinetic study:

**Study Number:** Naloxone-Ph1a-002

**Study Title:** "Phase 1, Pharmacokinetic Evaluation of Intranasal  
and Intramuscular Naloxone in Healthy Volunteers"

The inspection of the analytical portion of this study was conducted  
by (b) (4)

(b) (4) During the inspection, the OSIS scientists also  
audited the analytical portion of study (b) (4) supporting NDA  
(b) (4). The audit included a thorough examination of facilities and  
equipment, review of study records and correspondence, and  
interviews and discussions with (b) (4) management  
and staff. As a global assessment of the firm's bioanalytical  
operations, several key study components were selected for audit to  
assess the firm's overall bioanalytical operations and capability to  
conduct pharmacokinetic and/or bioequivalence studies.

At the conclusion of inspection, no objectionable conditions were  
observed related to the audit of study Naloxone-Ph1a-002. However,  
Form FDA 483 was issued for an observation pertaining to study (b) (4)  
(b) (4) for NDA (b) (4) (**Attachment 1**). This FDA 483 observation has no  
impact on study Naloxone-Ph1a-002 and will be discussed in a  
separate EIR review memo specific to NDA (b) (4). In addition to the  
FDA 483 observation, several items were discussed during the close-  
out meeting. The discussion items did not impact the data generated  
for study Naloxone-Ph1a-002.

The inspection of the clinical portion of study Naloxone-Ph1a-002  
was conducted by ORA investigator William Fred Lagud (KAN-DO) at  
Vince & Associates Clinical Research, Shawnee Mission, KS between  
October 1-19, 2015 and October 29, 2015. The audit covered a  
comprehensive review of regulatory files and study records,  
including study monitoring procedures and activities, personnel  
training, specimen handling and integrity, study protocols,  
subjects' records, informed consent forms, reporting of adverse  
events, and record retention.

At the conclusion of the inspection, Form FDA 483 was issued to  
Vince & Associates Clinical Research (**Attachment 2**). At the time of  
writing this review, OSIS has not received the response from Vince &  
Associates Clinical Research. We will submit an amended review when  
we evaluated the EIR and response from Vince & Associates. This  
review is based on our correspondences with the ORA Investigator,

exhibits collected during the inspection, and discussions between the ORA investigator with Vince & Associates management and staff during the inspection. The Form FDA 483 observations and our evaluation follow.

**Observation 1:**

**An investigation was not conducted in accordance with the investigational plan.**

**Specifically,**

**A. Naloxone-Phla-002 (v.2, 5 September 2014) protocol section 10.9.1, "Early Termination for an Individual Subject," item 1, lists a study subject respiratory rate <8 or >24 respirations per minute (r/m) among the criteria for terminating study participation for a single subject. No mention is made allowing for repeated measurements, although the source document designed by the study site allows for repeated measurements, per its Standard Operating Procedure (SOP).**

**On 06/Dec/2014, at 09:40 (the 30 min Supine Vital Signs measurement after dosing of the study drug), subject 01-02-039 experienced a respiration rate of 25 r/m (acceptable range: 9-20 r/m). The vitals were repeated at 10:12, with 25 r/m being measured again. A study Sub-Investigator was called and measured the vitals for a third time, documenting a reading of 24 r/m. The finding was documented by the Sub-Investigator as being not clinically significant (NCS) and the subject was allowed to continue participation in the study to its conclusion on 12/21/2014. The out-of-range values were not documented as an adverse event (AE).**

**OSIS Evaluation:**

The respirations per minute (r/m) of subject 01-02-039 increased to 25 r/m (acceptable range: 9-20 r/m) after dosing, and continued to remain at 25 r/m for approximately 30 minutes after dosing. A third measurement of respiration rate documented a reading of 24 r/m. According to the study protocol, the respiration rate should be measured (supine position) at approximately 60 minutes prior to dosing, and approximately 30, 60, 120, and 480 minutes after each naloxone dose. The subject did not experience any other significant respiration rate increase in other measurements. The site's SOP allows for repeated measurements. The finding was documented by the Sub-Investigator as being not clinically significant (NCS).

Although the above observation is not likely to impact the study outcome, the DAAAP medical reviewer should evaluate the impact of

this unreported adverse event (AE) on the safety evaluation of the investigational product.

**B. Naloxone-Phla-002 (v.2, 5 September 2014) protocol Attachment A: Procedure for Collection, Storage, and Delivery of Plasma Samples for Analysis of Naloxone Levels requires "There should be no more than 60 minutes between collection of the blood sample and placement of the plasma sample in the freezer."**

The Naloxone-Phla-002 PK Specimen Processing Log documents numerous Late to Freezer (LTF) samples, for example on study day 1, at predose, approximately 13 samples were documented as LTF (not placed in the -20°C freezer within 60 minutes); at 2.5 minutes approximately 6 samples were LTF; at 5 minutes approximately 10 samples were LTF. Of all samples collected on day one (12/02/2014), approximately 106 were documented as being placed in the freezer after 60 minutes (LTF); this does not include LTFs for the four other dosing/sample collection days.

The failure to place serum samples in the freezer within 60 minutes was not documented on the site's protocol deviation log, nor were any LTF-related occurrences reported to the Food and Drug Administration as protocol deviations.

**OSIS Evaluation:**

The firm failed to transfer a substantial number of PK samples to the -20°C freezer within 60 minutes of sample collection as specified in the study protocol. Additionally, the source data did not document the storage condition (e.g. on ice or at room temperature) of the collected blood samples before they were centrifuged. Although bench top stability was validated for 26 hours during method validation study for naloxone, this data was generated from frozen plasma samples. Stability in fresh plasma or in whole blood for naloxone was not established during method validation.

To assess the integrity of the "Late to Freezer (LTF)" samples, the analytical site for this study, (b) (4) was requested to design and conduct a benchtop stability study of Naloxone in human whole blood up to 60 minutes at both room temperature and 4°C. The plasma was to be transferred to the -20°C freezer after 30 minutes storage in refrigerator. The storage conditions in this experiment would mimic the sample handling procedure at the clinical site and would represent the worst-case scenario for these "Late to Freezer (LTF)" samples.

The results of this study were made available to the FDA investigators during the inspection and revealed that naloxone was

stable in whole blood for up to 60 minutes at room temperature and 4°C and for at least 30 min in plasma at refrigerated condition (**Attachment 3**). Therefore, Observation 1B is unlikely to impact the integrity of the naloxone concentration data.

**Observation 2:**

**Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.**

**Specifically,**

**A. Reported protocol deviations associated with late PK serum sample draws (LDs) are inaccurate, in that those listed on the firm's Protocol Deviation Log are not always technically protocol deviations when examined in source documentation, and other true protocol deviations found in source documentation are not always found on the protocol deviation log, thus were not reported to the Food and Drug Administration, for example:**

**I. For PK specimen draw time 2.5 minutes, three (3) late draws were observed on the PK Specimen Processing Log (subjects 02033, 02045, and 02075), although only two (2) were documented on the Protocol Deviation Log. According to protocol, three (3) were truly protocol deviations; two (2) late draws were reported to the FDA.**

**II. For PK specimen draw time 15 minutes, seven (7) late draws were observed on the PK Specimen Processing Log, although only five (5) were documented on the Protocol Deviation Log. According to protocol, seven (7) were truly protocol deviations; only five (5) were reported to the FDA.**

**III. For PK specimen draw time 300 minutes, three (3) late draws were observed on the PK Specimen Processing Log, although none (0) were documented on the Protocol Deviation Log. According to protocol, only one (1) was truly a protocol deviation; no (0) protocol deviations for 300 minute late draws on 12/02/2014 were reported to the FDA.**

**OSIS Evaluation:**

Discrepancies were observed between the reported protocol deviations and the source documents. Specifically, the protocol deviations submitted to the Agency (**Please refer to submission**) do not accurately represent the information from the PK Specimen Processing Log (**Attachment 4**).

We compared the data submitted to the Agency in the ADPC Study dataset to the data obtained from the source documents to verify the accuracy of the reported actual dosing and sampling times in the dataset. After comparing the actual dosing times, we conclude that the dosing times were accurately reported for all subjects. When we compared the sampling times for 2.5, 5, 10, 15, 20, 30 and 60 min post-dose for all treatments, we found discrepancies in the sampling times for three subjects (see table below). We request the OCP reviewer to include the actual sampling times in their pharmacokinetic analysis. This observation is unlikely to impact the outcome of the study because all the data except the examples below were accurately reported in the ADPC Study dataset.

Subject	Actual time reported	Actual time from source Data	Time Point	Dose	Period
NALOXONE-PH1A-002-VACR-02031	9:43AM	9:44AM	5 min	0.4mg	3
NALOXONE-PH1A-002-VACR-02033	9:44AM	9:49AM	5 min	2 mg	3
NALOXONE-PH1A-002-VACR-02045	10:57AM	10:55AM	60 min	2 mg	3

**B. Information documented in Adverse Events does not always correspond to applicable source documentation, for example:**

I. Subject 01-02040 was initially documented by Sub-Investigator (b) (4) as experiencing an AE lasting from 06 Dec 2014 to 08 Dec 2014 for "L Sided nostril pain and erythematous Septum pain. Bilat lower area of nasal septum". This AE was then documented as "Consolidated to one AE La 2-5-15." The subsequent (consolidated) Adverse Event form, also documented by Sub-Investigator (b) (4), documents, "Nasal Septal pain" and "Continuous Nasal Septum pain Constant" and "See Description from previous page - La". This AE documents the AE onset date as 06 Dec 2014 and the end date as 26 (or 21?) Dec 2014.

Nasal Irritation Scales from Day 5 (12/06/2014) to the Follow-Up visit were originally documented as "0" for "Normal appearing mucosa, no bleeding" or as "N/A," due to intramuscular injection dosing for that period. The Day 5 (12/6/14) and Day 6(12/7/14) Nasal Irritation Scales were edited to a "1" for "Inflamed mucosa, no bleeding" on 1/27/15 and 12/7/14, respectively.

II. Subject 01-02046 was documented on an Adverse Event form as experiencing Nasal Edema on 10 Dec 2014 by Sub-Investigator (b) (4). The

corresponding Nasal Irritation Exam (also documented by (b) (4) );  
however, documents "0" for "Normal appearing mucosa, no bleeding."

III. Subject 01-02056 was documented on an Adverse Event form as experiencing left nostril dryness with occasional bleeding in the mornings on 11 Dec 2014, ending 12 Dec 2014 by Sub-Investigator (b) (4) . The corresponding Nasal Irritation Exams (also documented by (b) (4) ), were both documented as "0" for "Normal appearing mucosa, no bleeding."

IV. Subject 01-02026 was documented on an Adverse Event form as experiencing Nasal edema on 10 Dec 2014 by Sub-Investigator (b) (4) . The corresponding Nasal Irritation Exam, (also documented by (b) (4) ) was originally documented as "0" for "Normal appearing mucosa, no bleeding." The information was edited by (b) (4) on 1/27/15 to document "1" for "Inflamed mucosa, no bleeding."

#### **OSIS Evaluation:**

The inaccurate documentation of Adverse Events for subjects 01-02040, 01-02046, 01-02056 and 01-02026 appears to have been corrected in part by the sub-investigator during the study conduct. Although the above observation is not likely to impact the study outcome, the DAAAP medical reviewer should evaluate the impact of the adverse events (AEs) on the safety evaluation of the investigational product

#### **Recommendations:**

- The DAAAP medical reviewer should evaluate the impact of Observations 1A and 2B on the impact of the overall safety of the investigational product.
- Following the evaluation of the inspectional findings, the data from the audited study were found to be reliable excluding the examples noted above. Thus, the reviewers recommend that the clinical and analytical data from study **Naloxone-Phla-002** be accepted for Agency review.

Arindam Dasgupta, Ph.D.  
Lead Pharmacologist  
DNDBE, OSIS

Yiyue Zhang, Ph.D.  
Visiting Associate  
DND BE, OSIS

Melkamu Getie-Kebtie, Ph.D., R.Ph.  
Staff Fellow  
DGDBE, OSIS

**Final Classification:**

**VAI - Vince & Associates Clinical Research (FEI# 3007544065)**  
**VAI -** (b) (4)

**\* The reviewers would like to acknowledge the contribution of Dr. Abhijit Raha with the data analysis.**

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah  
OTS/OSIS/DND BE/Bonapace/Dasgupta/Cho/Zhang/Raha  
OTS/OSIS/DGDBE/Haidar/Skelly/Choi  
CDER/OND/ODEII/DAAAP/Hertz  
ORA/(b) (4)/KAN-DO/(b) (4)/Lagud

Draft: YZ 10/27/2015 MGK 10/27/2015  
Edit: AD 10/30/2015, CB 10/30/2105  
ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/Vince & Associates Clinical Research, Shawnee Mission, KS

BE File#: (b) (4)

**FACTS: 11556176 (Vince & Associates Clinical Research)**

**FACTS** (b) (4)  
(b) (4)

328 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



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

/s/  
-----

ARINDAM DASGUPTA

10/30/2015

Please note that Arindam Dasgupta is also signing on behalf of Yiyue Zhang and Melkamu Getie-Keptie

CHARLES R BONAPACE

10/30/2015



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

---

Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Memorandum**

**Date:** September 28, 2015

**From:** Suchitra M. Balakrishnan, MD, PhD., Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health

**Through:** Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director  
Division of Pediatric and Maternal Health (DPMH)

**To:** Division of Anesthesia and Analgesia Products (DAAAP)

**Drug:** NARCAN (naloxone hydrochloride) Nasal Spray

**NDA/BLA:** NDA 208411  
**Applicant:** Adapt Pharma Operations Limited

**Subject:** Pregnancy and Lactation Labeling

**Proposed Indication:** emergency treatment of known or suspected opioid overdose

**Materials Reviewed:** Applicant's response to Information Request dated September 8, 2015  
Consult request dated August 5, 2015  
NDA 208411 Annotated Draft Labeling

**Consult Question:**  
"DAAAP is requesting that PMHS please assist us in reviewing the labeling for the new PLLR format."

## INTRODUCTION

Adapt Pharma has submitted a New Drug Application (NDA) for an intra- nasal (IN) formulation of naloxone hydrochloride (NDA 208411) being filed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. NDA 208411 relies on the previous findings of safety submitted in NDA 016636 for the reference listed drug, Narcan®, (naloxone hydrochloride) for injection. NDA 208411 is supported by two pharmacokinetic (PK) bioequivalence studies in healthy adult subjects. Additional clinical studies with naloxone hydrochloride via nasal administration have not been conducted. Cross-reference is made to the reference listed drug, Narcan, (naloxone hydrochloride) for injection. In addition, a review of the literature was conducted in search of new, relevant clinical data that was published since the approval of Narcan (1971).

Evzio® (Naloxone Auto-Injector) was approved in April, 2014. In addition, there are currently six generic naloxone drug products marketed, under ANDAs 070172, 070254, 070256, 070639, 072076 and 204997

This application was granted “Priority “review status with a user fee goal date of January 20, 2016. DAAAP consulted the DPMH Maternal Health Team (MHT) to review and update Section 8 of the proposed labeling to be in compliance with current regulatory requirements.

## BACKGROUND

### Drug Description

NARCAN nasal spray is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

Naloxone is a competitive opioid antagonist which interacts with all opioid receptors. It's highest affinity is for the  $\mu$  opioid receptor<sup>1,2</sup>. Naloxone is almost completely metabolized by the liver if given orally and therefore has to be administered parenterally. Naloxone is devoid of any agonist effect and is relatively lipid soluble with excellent CNS bioavailability<sup>2</sup>. Small doses of naloxone (0.4-0.8 mg) given intramuscularly or intravenously rapidly reverse the effects of exogenous opioids. Doses up to 5 to 10 mg of naloxone may be required to reverse the effect of potent opioids<sup>2</sup>.

The applicant indicates that doses of 2 and 4 mg IN produced naloxone plasma concentrations and exposures significantly higher than that noted when the same subjects received 0.4 mg IM. There were no differences between the routes and doses with respect to  $t_{max}$ , suggesting peak effects would occur at similar times for all treatments. Thus, use of the naloxone intranasal device delivering a target of 2 mg or 4 mg is purported to meet criteria

---

1 Yaksh TL, Wallace MS, Chapter 18. Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12e. New York: McGraw-Hill; 2011.

<http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266224> . Accessed September 29, 2015

2 Olson KR. Chapter 38. Poisoning. In: Papadakis MA, McPhee SJ, Rabow MW. eds. *CURRENT Medical Diagnosis & Treatment 2014*. New York: McGraw-Hill; 2014.

<http://accessmedicine.mhmedical.com/content.aspx?bookid=330&Sectionid=44291041>. Accessed September 29, 2015.

for an alternative to IM naloxone dosing. Plasma concentrations and overall exposure (AUC) are expected to be in the known efficacious range as compared to a clinical dose of IM naloxone.

### **Naloxone use in Pregnancy**

On September 8, 2015, the applicant submitted a summary of published human literature regarding fetal effects with maternal use of naloxone as requested at the mid-cycle meeting.

An important clinical adverse reaction observed in the literature postnatal is Neonatal Abstinence Syndrome (NAS)<sup>3</sup> or alternatively referred to as Neonatal Opiate Withdrawal Syndrome (NOWS). NAS is generally diagnosed in newborns of women using opioid agonists and can appear anywhere from day 1 to day 10 after birth. Symptoms of NAS are consistent with withdrawal from exposure to opioids with neurological excitability and autonomic/gastrointestinal dysfunction. They include excessive crying, blotchy skin color, diarrhea, hyperactive muscles, irritability, poor feeding, hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnea and bradycardia. Naloxone use can perpetuate symptoms of NAS in the fetus and neonate of mothers being treated chronically for opioid dependence

### **Applicants Review of Literature:**

#### *Pregnancy:*

The applicant cites one article by Hibbard *et al.*<sup>4</sup> reporting placental transfer of naloxone in pregnant women after IM or IV administration. In this study, maternal and umbilical venous serum naloxone concentrations were measured after the IV (n=30) or IM (n=7) injection of naloxone 400 µg. Following intravenous naloxone, there was rapid transfer to the fetus and therapeutic plasma concentrations could be expected in 1-2 minutes. Following intramuscular administration, neonatal concentrations were variable

The majority of articles found in the applicant's literature search focused on concomitant naloxone use with methadone and buprenorphine which are both partial agonists generally used in detoxification programs and are summarized further below.

Debelak *et al.* conducted a retrospective chart review which identified 10 opioid-dependent pregnant women treated with the buprenorphine plus naloxone film product between January 2010-June 2011<sup>5</sup>. Maternal findings were unremarkable, and reported to be comparable with what might be found following treatment with the buprenorphine-mono product. Neonates were full-term with normal birth parameters. Four neonates were treated for NAS, and number of days treated for NAS along with number of hospital days were in line with values reported for the buprenorphine-mono product.

---

3 Hudak, M., Tan, R., The Committee on Drug and the Committee on Fetus and Newborn. (2012). Neonatal Drug Withdrawal. Pediatrics, 129, e540. DOI: 10.1542/peds.2011-3212

4 Hibbard BM, Rosen M, Davies D. Placental transfer of naloxone. British journal of anaesthesia. 1986;58(1):45-8.

5 Debelak K, Morrone WR, O'Grady KE, Jones HE. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy-initial patient care and outcome data. Am J Addict. 2013;22(3):252-4.

A retrospective cohort analysis of 62 mother-neonate dyads treated with either buprenorphine and naloxone (n=31) or methadone (n=31) during pregnancy was conducted, comparing neonatal abstinence syndrome prevalence and characteristics among neonates<sup>6</sup>. Primary neonatal outcomes included diagnosis of neonatal abstinence syndrome, neonatal abstinence syndrome peak scores, total amount of morphine used to treat neonatal abstinence syndrome (mg), and duration of treatment for neonatal abstinence syndrome (days). Secondary outcomes included head circumference, birth weight, length, preterm birth, neonatal intensive care unit admission, Apgar scores, and overall length of hospitalization., from January 1, 2011, to November 30, 2013. Newborns exposed to maternal buprenorphine and naloxone had less frequent neonatal abstinence syndrome. Additionally, neonates exposed to buprenorphine and naloxone had shorter overall hospitalization lengths.

Lund *et al.* (2013) collected summary statistics on maternal and neonatal outcomes from seven previously published studies examining treatment for opioid-dependent pregnant women that represented a range of research methodologies<sup>7</sup>. Of these, randomized clinical trials are not available for naloxone containing treatments. Outcomes from these studies were compared to the same outcomes for 10 women treated with the combined buprenorphine plus naloxone product (reference 5). They report that there are no suggestions of significant adverse maternal or neonatal outcomes related to the use of buprenorphine plus naloxone for the treatment of opioid dependence during pregnancy. However, further research should examine possible differences between buprenorphine plus naloxone and buprenorphine alone or methadone in fetal physical development.

Gawronski KM, *et al* conducted a retrospective review of clinical and demographic information of 58 infants whose mothers were treated with buprenorphine/naloxone and 92 infants whose mothers were treated with methadone for opioid dependence during pregnancy<sup>8</sup>. Neonatal abstinence syndrome occurred less frequently among infants of mothers treated with buprenorphine/naloxone than those treated with methadone (64% and 80%, respectively,  $p = 0.03$ ). All infants with neonatal abstinence syndrome were treated postnatally with methadone. There was a trend toward shorter duration of treatment and lower cumulative dosages of methadone among the buprenorphine/naloxone-exposed infants.

#### *Labor and Delivery:*

The studies listed in the applicant's literature review examined the effects of naloxone on opioid induced pruritus and nausea and post-operative analgesia during labor and delivery. No significant effects are reported. Van Vonderen *et al.* published a respiratory recording (using a combination of a pulse oximeter, respiratory monitor and digital video recorder) of an infant during resuscitation in the delivery room after receiving naloxone for respiratory depression, resulting from maternal remifentanyl use<sup>9</sup>. The infant was born apneic and

---

6 Wiegand SL, Stringer EM, Stuebe AM, Jones H, Seashore C, Thorp J. Buprenorphine and naloxone compared with methadone treatment in pregnancy. *Obstetrics and gynecology*. 2015;125(2):363-8.

7 Lund IO, Fischer G, Welle-Strand GK, O'Grady KE, Debelak K, Morrone WR, et al. A Comparison of Buprenorphine + Naloxone to Buprenorphine and Methadone in the Treatment of Opioid Dependence during Pregnancy: Maternal and Neonatal Outcomes. *Substance abuse : research and treatment*. 2013;7:61-74.

8 Gawronski KM, Prasad MR, Backes CR, Lehman KJ, Gardner DK, Cordero L. Neonatal outcomes following in utero exposure to buprenorphine/naloxone or methadone. *SAGE Open Medicine*. 2014;2.

bradycardic. Normal resuscitation maneuvers had no effect on the respiratory drive. Directly after administration of naloxone, a tachypneic breathing pattern with sporadic expiratory breaking maneuvers was observed, which was consistent with the pharmacological effect of naloxone.

Hodgkinson *et al.* (1978) conducted a study in which an early neonatal neurobehavioral scale was administered to three groups of newborns at 2, 4, and 24 hours of age. Group 1 consisted of 28 neonates whose mothers had received no narcotics during labor, Group 2 of 33 neonates whose mothers had received meperidine hydrochloride alone during labor, and Group 3 of 40 neonates whose mothers had received meperidine followed by 0.4 mg of naloxone hydrochloride intravenously approximately 15 minutes before delivery. Neonates who were not exposed to meperidine showed a statistically significantly greater percentage of high scores than those exposed to meperidine alone for all items on the neurobehavioral scale at 2 and 4 hours and for all items except tone and Moro response at 24 hours. Similarly, neonates whose mothers had received meperidine and naloxone showed a significantly greater percentage of high scores than those whose mothers had received meperidine alone at 2 hours of age. At 4 hours a difference was found for tone and rooting and at 24 hours for overall score, placing, and total decrement score.

#### *Lactation:*

The applicant submitted clinical studies supporting no blunting effects of naloxone on the prolactin response to suckling<sup>10</sup> and the release of oxytocin or vasopressin in response to breast feeding and breast stimulation in humans<sup>11</sup>.

#### *Applicant's Conclusions:*

"There are no adequate and well-controlled studies with NARCAN nasal spray in pregnant women. However, findings published in literature since the approval of naloxone suggest that there are no obvious significant adverse maternal or neonatal outcomes related to the use of naloxone for the treatment of opioid dependence during pregnancy.

Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus as well as in the opioid-dependent mother.

Although studies in lactating mothers have been conducted, none of the studies specifically looked for naloxone in the milk. Therefore, it is not known if naloxone hydrochloride is present in human milk. However, naloxone does not affect suckling-induced secretion of oxytocin or prolactin in postpartum women."

#### *Reviewer's Comment:*

---

9 van Vonderen JJ, Siew ML, Hooper SB, de Boer MA, Walther FJ, te Pas AB. Effects of naloxone on the breathing pattern of a newborn exposed to maternal opiates. *Acta paediatrica* (Oslo, Norway : 1992). 2012;101(7):e309-12.

10 Cholst IN, Wardlaw SL, Newman CB, Frantz AG. Prolactin response to breast stimulation in lactating women is not mediated by endogenous opioids. *American journal of obstetrics and gynecology*. 1984;150(5 Pt 1):558-61.

11 Johnson MR, Andrews MA, Seckl JR, Lightman SL. Effect of naloxone on neurohypophyseal peptide responses to breast feeding and breast stimulation in man. *Clinical endocrinology*. 1990;33(1):81-6.

*The applicant's conclusions seem reasonable; there are no adequate and well controlled studies examining naloxone use in pregnancy and there appear to be no reasons for discontinuing breast-feeding secondary to naloxone use per se. DPMH has also reviewed naloxone use in pregnancy and lactation with prior submissions and came to similar conclusions<sup>12, 13</sup>.*

## **DISCUSSION**

### **Pregnancy and Lactation Labeling**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>14</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>15</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

### **Nonclinical Experience**

The REPROTOX® database indicates that use of naloxone during pregnancy is not expected to increase the risk of congenital anomalies<sup>16</sup>. It cites studies in which mice and hamsters were given naloxone during pregnancy. No teratogenicity was observed even with doses of naloxone 2500 to 20,000 times (in mice) and 9200 to 98,000 times (in hamsters) the dose used for single injections in humans. REPROTOX® does report there were some behavioral changes from prenatal naloxone exposure in rats; however, these changes in rats did not occur in a dose-dependent manner and only some of them persisted into adulthood<sup>17</sup>.

*Reviewer's Comment: The applicant proposes inclusion of the same nonclinical data in section 8 of the Narcan Nasal Spray label as the RLD (See excerpt below.) No nonclinical data are reported evaluating the effects of naloxone on lactation. DPMH will defer to the DAAAP non-clinical team regarding the final nonclinical information included in the labeling. .*

---

12 DPMH review for Evzio® (Naloxone auto-injector), NDA 205787, by Dr. Carol H. Kasten dated March 30, 2014, (DARRTs reference ID 3479745)

13 DPMH review for Movantik (naloxegol oxalate), NDA 204760, by Dr Carrie Ceresa dated May 14, 2014, (DARRTs reference ID-3506381).

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

15 *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

16 Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies.

17 Shepanek NA, Smith RF, Tyler ZE, et al.: Behavioral and neuroanatomical sequelae of prenatal naloxone administration in the rat. *Neurotoxicol Teratol* 11:441-446, 1989

*Source: Prescribing Information for Narcan® (naloxone hydrochloride) for injection.*

**Pregnancy:** Naloxone hydrochloride was administered during organogenesis to mice and rats at doses 4-times and 8-times, respectively, the dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m<sup>2</sup>). These studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

**Mutagenesis** Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.

**Impairment of Fertility:** Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m<sup>2</sup>), demonstrated no adverse effect of naloxone hydrochloride on fertility.

### **Clinical Experience:**

#### **Pregnancy:**

In addition to the article cited by the applicant <sup>4</sup>, additional studies have reported that naloxone administered to the mother rapidly crosses the placenta to the fetus. An *in vitro* human placental perfusion study has demonstrated naloxone rapidly crosses the placenta within 2 minutes after maternal administration<sup>18</sup>. In a placebo controlled study of 54 non-opioid dependent pregnant women near term, the women were administered 0.4 mg of naloxone. In the first hour following administration, increased gross fetal body and breathing movements were significantly increased consistent with rapid transplacental transfer of the drug. The authors commented that their data suggest endogenous endorphins may be involved in modulation of fetal behavior<sup>19</sup>.

The applicant proposed labeling indicates that there are no adequate data available about naloxone use in pregnant women to inform about drug-associated risk and advises that naloxone should be used in pregnancy only when clearly needed. The labeling also describes the risk for neonatal withdrawal syndrome under *Clinical Considerations*.

DPMH finds there is insufficient information to make a clear assessment of risk since there are no adequate data regarding naloxone use in pregnant women

#### **Lactation**

A review of Hale's Medications and Mother's Milk reveals that naloxone is poorly absorbed orally<sup>20</sup>. A search of published literature in the Drugs and Lactation Database (LactMed) for available human lactation data was also performed to update the Lactation subsection of labeling for this application. The Drugs and Lactation Database (LactMed)<sup>21</sup> states no

---

18 Kopecky EA, Simone C, Knie B, Koren G: Transfer of morphine across the human placenta and its interaction with naloxone. *Life Sci* 1999;65:2359-71.

19 Arduini D, Rizzo G, Dell'Acqua S et al. Effect of naloxone on fetal behavior near term. *Am J Obstet Gynecol* 1987 Feb;156:474-8.

20 Hales's 2012 Medications and Mother's Milk, 15<sup>th</sup> edition, Amarillo, TX

21 The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed provides information, when available, on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known,



information is available on the presence of naloxone in breast milk, concurs with Hale's that it is not orally bioavailable, and also states that oxytocin and prolactin secretion during breast feeding are not affected.

#### **Females and Males of Reproductive Potential:**

Non clinical studies described in Section 13.1 are not suggestive of any effect on fertility. In the absence of human data, DPMH agrees that this section is not required in the package insert.

#### **CONCLUSIONS**

NARCAN (naloxone hydrochloride) nasal spray labeling has been updated to comply with the PLLR. A review of the published literature revealed no adequate data regarding naloxone use in pregnant or lactating women. DPMH has the following recommendations for Narcan nasal spray labeling:

- **Pregnancy, Section 8.1**

- The "Pregnancy" subsection of Narcan nasal spray labeling was formatted in the PLLR format to include "Pregnancy Registry," "Risk Summary," "Clinical Considerations," and "Data" subsections<sup>22</sup>.

- **Lactation, Section 8.2**

- The "Lactation" subsection of Narcan nasal spray labeling was formatted in the PLLR format to include the "Risk Summary" subsection<sup>23</sup>.

#### **RECOMMENDATIONS**

- 1.) DPMH revised subsections 8.1 and 8.2 in Narcan nasal spray labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

#### **8.1 Pregnancy**

##### Risk Summary

The limited available data on naloxone use in pregnant women are not sufficient to inform a drug associated risk. However there are clinical considerations [*see Clinical Considerations*]. In animal reproduction studies, there were no embryotoxic effects when naloxone hydrochloride was administered during organogenesis in mice and rats at doses 4-times and 8-times, respectively, as compared to an intravenous dose of 10 mg/day given to a 50 kg human. [*see Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of

---

alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

<sup>22</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

<sup>23</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

### Clinical Considerations

#### *Fetal/Neonatal adverse reactions*

Naloxone hydrochloride crosses the placenta, and may precipitate withdrawal in the fetus, as well as in the opioid-dependent mother [see *Warnings and Precautions (5.4)*]. The fetus should be evaluated for signs of distress after NARCAN is used. Careful monitoring is needed until the fetus and mother are stabilized.

### Data

#### *Animal Data*

Naloxone hydrochloride was administered during organogenesis to mice and rats at doses 4-times and 8-times, respectively, as compared to an intravenous dose of 10 mg/day given to a 50 kg human (when based on body surface area or mg/m<sup>2</sup>). These published studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride [see *Nonclinical Toxicology (13.1)*].

## **8.2 Lactation**

### Risk Summary

There is no information regarding the presence of naloxone in human milk, or the effects of naloxone on the breastfed infant or on milk production. Studies in nursing mothers have shown that naloxone does not affect prolactin or oxytocin hormone levels. Naloxone is minimally orally bioavailable. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for NARCAN and any potential adverse effects on the breastfed infant from NARCAN or from the underlying maternal condition.

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

/s/  
-----

SUCHITRA M BALAKRISHNAN  
10/19/2015

TAMARA N JOHNSON  
10/19/2015

LYNNE P YAO  
10/26/2015

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

---

**Date of This Memorandum:** October 13, 2015  
**Requesting Office or Division:** Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)  
**Application Type and Number:** NDA 208411  
**Product Name and Strength:** Narcan Nasal Spray (naloxone hydrochloride) nasal spray  
4 mg per 0.1 mL  
**Submission Date:** October 8, 2015  
**Applicant/Sponsor Name:** Adapt Pharma, Inc.  
**OSE RCM #:** 2015-1532  
**DMEPA Primary Reviewer:** Millie Shah, PharmD, BCPS  
**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

---

#### 1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container label, blister labeling, carton labeling and Quick Start Guide (QSG) for Narcan Nasal Spray (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1,2</sup>

---

<sup>1</sup> Shah M. Human Factors, Label, and Labeling Review for Narcan Nasal Spray (NDA 208411). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 03. 35 p. OSE RCM No.: 2015-1531 and 2015-1532.

<sup>2</sup> Shah M. Memorandum Review of Revised Label and Labeling for Narcan Nasal Spray (NDA 208411). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 25. 6 p. OSE RCM No.: 2015-1531 and 2015-1532.

## **2 CONCLUSION**

The revised container label, blister labeling, and carton labeling for Narcan Nasal Spray are acceptable from a medication error perspective. However, the revised Quick Start Guide (QSG) is unacceptable from a medication error perspective. Thus, we provide recommendations for the Applicant below.

## **3 RECOMMENDATIONS FOR ADAPT PHARMA, INC.**

We recommend the Applicant implement the following prior to approval of this NDA:

### **A. Quick Start Guide (QSG)**

1. The word “overdose” is misspelled as “overdoes” under the heading “Quick Start Guide.” Correct the spelling of the misspelled word.

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

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

/s/  
-----

MILLIE C BRAHMBHATT  
10/13/2015

BRENDA V BORDERS-HEMPHILL  
10/13/2015

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

---

<b>Date of This Memorandum:</b>	September 25, 2015
<b>Requesting Office or Division:</b>	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
<b>Application Type and Number:</b>	NDA 208411
<b>Product Name and Strength:</b>	Narcan Nasal Spray (naloxone hydrochloride) nasal spray 4 mg per 0.1 mL
<b>Submission Date:</b>	September 23, 2015
<b>Applicant/Sponsor Name:</b>	Adapt Pharma, Inc.
<b>OSE RCM #:</b>	2015-1532
<b>DMEPA Primary Reviewer:</b>	Millie Shah, PharmD, BCPS
<b>DMEPA Team Leader:</b>	Vicky Borders-Hemphill, PharmD

---

## 1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container label, blister labeling, carton labeling and Quick Start Guide (QSG) for Narcan Nasal Spray (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

## 2 CONCLUSION

The revised container label, blister labeling, and carton labeling are unacceptable from a medication error perspective. Thus, we provide recommendations for the Applicant below.

<sup>1</sup> Shah M. Human Factors, Label, and Labeling Review for Narcan Nasal Spray (NDA 208411). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 03. 35 p. OSE RCM No.: 2015-1531 and 2015-1532.

### 3 RECOMMENDATIONS FOR ADAPT PHARMA, INC.

We recommend the Applicant implement the following prior to approval of this NDA:

A. Container label (single and two-pack)

1. As currently presented, the expiration date is in the format “MMMY.” We recommend 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:<sup>2</sup> MMMYYYY (e.g., JAN2015) or MMMDDYYYY (e.g., JAN012015).

B. Blister labeling (single and two-pack)

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

C. Carton Labeling (single and 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/thought it contained 2 doses.

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

---

<sup>2</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.



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

/s/  
-----

MILLIE C BRAHMBHATT  
09/25/2015

BRENDA V BORDERS-HEMPHILL  
09/25/2015

**MEMORANDUM**

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

---

DATE: August 25, 2015

TO: Director, Investigations Branch  
ORA Kansas City District Office  
11630 W. 80th St.  
Lenexa, KS 66214

FROM: Charles R. Bonapace, Pharm.D.  
Director  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **FY 2015, CDER High Priority Pre-Approval Data  
Validation Inspection**, Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 208411  
DRUG: Naloxone Hydrochloride Intranasal Spray  
SPONSOR: Adapt Pharma Operations Limited, Dublin, Ireland

This inspection memo provides pertinent information to conduct the inspection of the clinical portion of the following bioavailability study. Background material is available in ECMS under the ORA folder. **Please note that this is a CDER high-priority assignment and the inspection should be completed and endorsed EIR submitted to CDER prior to October 8, 2015.**

**Do not reveal the studies to be inspected, drug names, or the study investigators to the site prior to the start of the inspections.** The site will receive this information during the inspection opening meeting. The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

**At the completion of the inspection, please send a scanned copy of the completed section A of this memo to the OSIS POC.**

**Study Number:** Naloxone-Ph1a-002

**Study Title:** "Phase 1, Pharmacokinetic Evaluation of Intranasal and Intramuscular Naloxone in Healthy Volunteers."

**Clinical Site:** Vince Associates Clinical Research  
10103 Metcalf Avenue  
Overland Park, KS 66212  
Tel: (913) 696-1601  
Fax: (913) 696-1640

**Investigator:** Martin Kankam, M.D., Ph.D.

**# of Subjects:** 30

**Because Study Naloxone-Ph1a-002 is not a bioequivalence study, reserve samples of the test article and reference product should not be collected.**

#### **SECTION A - CLINICAL DATA AUDIT**

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

##### **Data Audit Checklist:**

- ☐ Confirm that informed consent was obtained for all subjects enrolled at the site
- ☐ Audit the study records for all subjects enrolled at the site.
- ☐ Compare the study report submitted to FDA with the original documents at the site.
- ☐ Check for under-reporting of adverse events (AEs).
- ☐ Check for evidence of inaccuracy in the electronic data capture system.
- ☐ Check reports for the subjects audited.
  - o Number of subject records reviewed during the inspection:\_\_\_\_\_
  - o Number of subjects screened at the site:\_\_\_\_\_
  - o Number of subjects enrolled at the site:\_\_\_\_\_
  - o Number of subjects completing the study:\_\_\_\_\_
- ☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.

- ☐ Confirm that site personnel followed SOPs during study conduct.
- ☐ Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- ☐ Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).
- ☐ Include a brief statement summarizing your findings including IRB approvals, study protocol, and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- ☐ Other comments:

---

---

---

**Additional instructions to the ORA Investigator:**

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

**If you issue Form FDA 483, please forward a copy to the OSIS POC (see below). If it appears that the observations may warrant an OAI classification, notify the OSIS POC as soon as possible. Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the OSIS POC.**

**OSIS POC:** Yiyue Zhang, Ph.D.  
Division of New Drug Bioequivalence Evaluation (DND BE)  
Office of Study Integrity and Surveillance (OSIS)  
Tel: (240) 402-6559  
Fax: (301) 847-8748  
E-mail: [yiyue.zhang@fda.hhs.gov](mailto:yiyue.zhang@fda.hhs.gov)

**The endorsed EIR should be sent to the following address:**

Ms. Venese Dejernett  
FDA/CDER/DBGLPC  
W051 RM5318 HFD-45  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  
1-301-796-0650  
venese.dejernett@fda.hhs.gov

Email cc:

ORA/SW-FO/KAN-DO/KAN-IB/Bromley  
OSIS/Taylor/Dejernett/Fenty-Stewart/Nkah/Johnson  
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Zhang  
OSIS/DGDBE/Haidar/Skelly/Choi

Draft: YZ 8/24/2015

Edit: AD 8/25/2015; CB 08/25/2015

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/Vince Associates Clinical Research, Overland Park, KS

BE File#:6942

**FACTS: 11556176**

Yiyue Zhang -S

Digitally signed by Yiyue Zhang -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
cn=Yiyue Zhang -S, 0.9.2342.19200300.100.1.1=2001741289  
Date: 2015.08.25 07:33:17 -04'00'

Yiyue Zhang, Ph.D.  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

Arindam Dasgupta -S

Digitally signed by Arindam Dasgupta -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, 0.9.2342.19200300.100.1.1=0012329705,  
cn=Arindam Dasgupta -S  
Date: 2015.08.25 08:45:22 -04'00'

Arindam Dasgupta, Ph.D.  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

Charles R.  
Bonapace -S

Digitally signed by Charles R. Bonapace -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People,  
0.9.2342.19200300.100.1.1=1300156609,  
cn=Charles R. Bonapace -S  
Date: 2015.08.25 08:56:27 -04'00'

Charles Bonapace, Pharm.D.  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

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

/s/  
-----

YIYUE ZHANG  
09/17/2015

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 208411 BLA#	NDA Supplement #: S- BLA Supplement #: S-	<b>Efficacy Supplement Category:</b> <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: NARCAN (naloxone hydrochloride) Nasal Spray Established/Proper Name: Naloxone hydrochloride Dosage Form: liquid, intranasal spray Strengths: 4 mg		
Applicant: Adapt Pharma Operations Limited Agent for Applicant (if applicable): Richard E. Lowenthal, Pacific Link Consulting		
Date of Application: July 17, 2015 Date of Receipt: July 20, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: January 20, 2016		Action Goal Date (if different): November 20, 2015
Filing Date: September 18, 2015		Date of Filing Meeting: August 13, 2015
<b>Chemical Classification (original NDAs only) :</b> <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input checked="" type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication: Treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		



Type of BLA		<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)		
<b><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i></b>				
Review Classification:		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority		
<b><i>The application will be a priority review if:</i></b> <ul style="list-style-type: none"> <li><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i></li> <li><i>The product is a Qualified Infectious Disease Product (QIDP)</i></li> <li><i>A Tropical Disease Priority Review Voucher was submitted</i></li> <li><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></li> </ul>		<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input checked="" type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>		<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)		
<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 114704				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <b><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i></b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <b><i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i></b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

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

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

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

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>



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

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

<b><u>PREA</u></b> Does the application trigger PREA? <i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC meeting has been scheduled.
<b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b><u>BPCA:</u></b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Separate submission was sent to DMEPA.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not required for this product.
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

2

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

3

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

Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The review was requested and the Applicant has submitted the required information to the NDA.
<b>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consulted to DMMP (Patient Labeling)
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL)			

4

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

5

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



	<input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH and CDRH Compliance - consulted August 5, 2015.
<i>If yes, specify consult(s) and date(s) sent:</i>				Clinical Pharmacology Inspections consult sent 7/21/2015
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> March 27, 2015	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Minutes dated 4/20/2015
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

# ATTACHMENT

## MEMO OF FILING MEETING

**DATE:** August 13, 2015

**BACKGROUND:** This NDA will be reviewed under a 4-month clock.

### **REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diana Walker	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Joshua Lloyd		Y
Division Director	Sharon Hertz		Y
Office Director/Deputy	Curtis Rosebraugh		N
Clinical	Reviewer:	Joshua Lloyd	Y
	TL:	Joshua Lloyd	Y
Clinical Pharmacology	Reviewer:	Suresh Naraharisetti	Y
	TL:	Yun Xu	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carlic Huynh	N
	TL:	Newton Woo Daniel Mellon	N Y
Product Quality (CMC) Review Team:	ATL:	Ciby Abraham	Y
	RBPM:	Steve Kinsley	Y
• Drug Substance	Reviewer:	Venkateswara Pavuluri	Y
• Drug Product	Reviewer:	Venkateswara Pavuluri	Y
• Process	Reviewer:	Edwin Jao	Y
• Microbiology	Reviewer:	Christina Capacci-Daniel	Y
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:	Tapash Ghosh	N
• Other (e.g., Branch Chiefs, EA Reviewer)	Branch Chief: Julia Pinto		Y
	OPQ Chief: Eric Duffy		N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Nathan Caulk	Y
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Shenee' Toombs	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Millie Shah	Y
	TL:	Vicky Borders-Hemphill	N

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
CDRH	Reviewer:	Ryan McGowan	N
	TL:	Richard Chapman	Y
Other reviewers/disciplines			
• <b>Discipline</b>	Reviewer:		
	TL:		
Other invitees	OSI – Patricia Love and Bindi Nikhar		N
	OCOMM – Morgan Jerrick		Y

#### **FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>A BA/BE study was done to bridge to the NARCAN NDA. There was additional discussion about the fact that the Applicant recently became the owner of the NDA they are referencing, NARCAN. The review team is looking at whether this is a 505(b)(2) NDA based on literature.</p>
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> No comments</p>

<p><b>CLINICAL</b></p> <p><b>Comments:</b> Minor review issues were sent to the Applicant as information requests, and responses were received and found adequate.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no,</b> explain: There were no clinical sites, however, the sites of the BA/BE studies will be inspected because they are the pivotal studies.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="text"/> <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

--	--

APPEARS THIS WAY ON ORIGINAL

<b>CLINICAL PHARMACOLOGY</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES – consults had been sent prior to the Filing meeting. <input type="checkbox"/> NO
<b>BIOSTATISTICS</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b> Minor review issues were sent to the Applicant as information requests, and responses were received and found adequate.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b> OPQ Information Requests were sent to the Applicant and responses have been received. CDRH Information Requests were sent to the Applicant and responses are pending at the time of this review.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b><u>New Molecular Entity (NDAs only)</u></b>  <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b><u>Environmental Assessment</u></b>  <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

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



REGULATORY PROJECT MANAGEMENT	
<p><b>Signatory Authority:</b> Sharon Hertz, MD, Director, DAAAP</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): September 24, 2015</p> <p><b>21<sup>st</sup> Century Review Milestones:</b> Wrap-up: October 22, 2015</p> <p>Comments: note that we are planning a 4-month action date, so these milestone meetings are based on this date. If issues arise that a 4-month date is not possible, these meeting dates may be revised to fit the 6-month timeline.</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. (<b>Note: requests for additional information were identified for OPQ, CDRH, and clinical and sent to the Applicant prior to the 74-day letter in order to expedite review.</b>)</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTION ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/  
-----

DIANA L WALKER  
09/10/2015

# **REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208411

**Application Type:** New NDA

**Name of Drug/Dosage Form:** NARCAN (naloxone hydrochloride) nasal spray, 4 mg

**Applicant:** Adapt Pharma

**Receipt Date:** July 20, 2015 and updated labeling July 31, 2015 (to add PLLR format)

**Goal Date:** November 20, 2015 (PDUFA = January 20, 2016)

## **1. Regulatory History and Applicant's Main Proposals**

This is a new NDA. NARCAN (naloxone hydrochloride) nasal spray, 4 mg, is indicated for treatment of opioid overdose.

## **2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## **3. Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Pregnancy category should be removed under the new PLLR format rules.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format and the resubmitted PI will be used for further labeling review.

## Selected Requirements of Prescribing Information

### Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

### Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

#### HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:** *Margins were incorrect and have been changed to 1/2 inch.*

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:** *Some statements in Indications and Usage are not referenced.*

*Applicant will be asked to correct this.*

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

## Selected Requirements of Prescribing Information

• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

**Comment:** *Applicant had inserted month also, this will be deleted.*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

### Comment:

## Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

### Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

## Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

## Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:



## Selected Requirements of Prescribing Information

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

*Comment:*

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report **SUSPECTED ADVERSE REACTIONS**, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)”.

*Comment:*

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “See 17 for **PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**”

*Comment:*

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:*

## Selected Requirements of Prescribing Information

---

### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

**YES** 25. The TOC should be in a two-column format.

*Comment:*

**YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

*Comment:*

**YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

*Comment:*

**YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

*Comment:*

**YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

*Comment:*

**NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

*Comment:* *The subheadings do not match those in the FPI in some sections.*

*The Applicant will be asked to correct these.*

**YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”

*Comment:*



## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

**N/A**

## Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- N/A** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

[text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/  
-----

DIANA L WALKER  
09/10/2015

---

## HUMAN FACTORS, LABEL, AND LABELING REVIEW

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

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

---

<b>Date of This Review:</b>	September 3, 2015
<b>Requesting Office or Division:</b>	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
<b>Application Type and Number:</b>	NDA 208411
<b>Product Name and Strength:</b>	Narcan (naloxone hydrochloride) nasal spray 4 mg per 0.1 mL
<b>Product Type:</b>	Single-ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Adapt Pharma, Inc.
<b>Submission Date:</b>	June 19, 2015
<b>OSE RCM #:</b>	2015-1531 and 2015-1532
<b>DMEPA Primary Reviewer:</b>	Millie Shah, PharmD, BCPS
<b>DMEPA Team Leader:</b>	Vicky Borders-Hemphill, PharmD
<b>Human Factors Specialist:</b>	Quynh Nhu Nguyen, MS
<b>DMEPA Associate Director:</b>	Irene Chan, PharmD, BCPS

---

## 1 REASON FOR REVIEW

Adapt Pharma, Inc. submitted their human factors validation study, labels, and labeling for Narcan (naloxone hydrochloride) nasal spray. Narcan is a nasal spray device that contains naloxone for the emergency treatment of opioid overdose. Thus, the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the human factors validation study, container labels, carton labeling, and prescribing information to determine if they are acceptable from a medication error perspective.

## 2 MATERIALS REVIEWED

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

<b>Table 1. Materials Considered for this Human Factors, Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study (1 device 4 mg)	C
ISMP Newsletters	D- (N/A)
FDA Adverse Event Reporting System (FAERS)*	E- (N/A)
Information Request and Human Factors Study (2 devices 2 mg each)	F
Labels and Labeling	G
Prescribing Information	H

N/A=not applicable for this review

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

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Narcan (naloxone hydrochloride) nasal spray will be supplied as a single nasal spray device in a blister. Each nasal spray device contains 4 mg per 0.1 mL. One dose requires one spray in one nostril. (b) (4)

### Human Factors Summative Study Assessment

We evaluated the human factors summative study, which was conducted with 53 participants who were representative of the intended user group, which consists of the general population of individuals 12 years and older and low literacy lay users. The participants were untrained on use of the device. Of the 53 participants, five (5) participants did not successfully complete one

of the two critical tasks of inserting the nozzle into the nostril and pressing the plunger to release the dose in the nose:

- Two of the five participants administered the dose into the mouth of the overdose victim (mannequin). The Applicant's root cause analysis indicated that one of the participants used common sense rather than reading the IFU, and the other participant thought that they only saw one opening on the mannequin, which was the mouth. None of the root causes were attributed to the product design or labeling.
- Two of the five participants did not press the plunger completely to release the dose. The Applicant's root cause analysis showed that these participants were confused by the setting of simulation, and attributed these failures to study artifacts.
- One of the five participants expelled the product into the air prior to inserting it into the nasal opening. The participant indicated that he was trying to test how hard to push the plunger prior to administering to the mannequin.

We reviewed the product labeling (carton labeling, Instructions for Use (IFU), and Quick Start Guide (QSG)) to evaluate the clarity and prominence of the information regarding the correct site of administration and information about not testing the device before use. We did not identify any specific concerns with the proposed labels and labeling; however, revising the statement to highlight for use in the nose only on the blister labeling may help to further reduce the risk for wrong site of administration errors.

We also reviewed the results of the other secondary tasks; however, those tasks were part of emergency response and did not require the user to interact with the proposed product. Therefore, we do not have any comments regarding the secondary tasks.

We noted that the study also evaluated users' comprehension of critical information contained in the Patient Information section. The question regarding withdrawal symptoms had a lower number of correct responses due to participants not recalling all of the information. Subsequently, the Sponsor made formatting changes to increase the prominence of the withdrawal symptoms. There were other exploratory questions that were included as part of the comprehension assessment such as *Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL, or Will TRADENAME NASAL have any effect in people who are not taking opioid medicines.* These two questions received a lower score due to most participants not focusing on the entirety of the section being questioned, not being able to locate the information, or being focused on the pregnancy warning (which was correct), but missing the other warnings, or being unfamiliar with the term 'opioids'. Our review of the Patient Information section determined that no additional changes are necessary to improve comprehension. Additionally, this information is the same that is presented for another currently marketed naloxone product intended for administration by the general population, and we are not aware of any postmarketing concerns surrounding this information.



### **Labels, Labeling, and Packaging Assessment**

We find the packaging configurations that contain (b) (4) 2 nasal spray devices per container acceptable. Our review of the container labels, blister labeling, and carton labeling identified several deficiencies that the Applicant will need to address. Specifically we identified issues with the prominence of the established name, expiration date, prominence of the strength, and lack of usual dose statement. Thus, we provide recommendations in Section 4.2 to correct these deficiencies.

Our review of the prescribing information determined that some of the information in the Instructions for Use (IFU) does not correspond exactly with the instructions on the Quick Start Guide (QSG). Since the human factors validation study used the instructions on the QSG, we recommend the instructions in the IFU located at the end of the *Patient Information* section exactly match the instructions on the QSG. Furthermore, Step 3 of the IFU, (b) (4) does not provide instructions on how long to wait before administering an additional dose of Narcan nasal spray. Per our discussion with the DAAAP medical officer, users should wait 2 to 3 minutes before administering an additional dose. Additionally, we determined the fourth bullet under the section “*What is the most important information I should know about Narcan nasal spray?*” does not include the amount of time to wait prior to administering an additional dose. We have included specific recommendations in Section 4.1 for the review Division to consider.

Our review of the *Dosage and Administration*, *Dose Forms and Strength*, *How Supplied*, and *Patient Counseling Information* sections determined that they are acceptable from a medication error perspective

## **4 CONCLUSION & RECOMMENDATIONS**

### **Human Factors**

We find that the Human Factors validation study report provides sufficient data to conclude that the product can be used safely and effectively by intended users for intended uses and environments.

### **Labels and Labeling**

We identified areas in the proposed labels and labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product. These changes to the user interface do not require an additional human factors validation study.

If you have further questions or need clarifications, please contact Lisa Skarupa, OSE Project Manager, at 301-796-2219.

#### 4.1 RECOMMENDATIONS FOR THE DIVISION

We have revised the *Patient Information* section of the Full Prescribing Information (See Appendix H) and have provided a detailed summary below for review and consideration by DAAAP.

##### A. Patient Information

1. We recommend that the Instructions for Use (IFU) located at the end of this section are consistent with the instructions located on the carton labeling and Quick Start Guide (QSG), since these instructions were used in the human factors validation study. The step “ (b) (4) ,” which is present on the carton labeling and QSG is missing on the IFU. Therefore, we recommend including this step and corresponding figure.
2. We recommend bullet number 4 under the section *What is the most important information I should know about Narcan nasal spray?* be revised from, “If this happens, (b) (4) (b) (4) should be closely watched until emergency help is received.” to, “If this happens, an additional dose using a new NARCAN single use nasal device may be given after 2 to 3 minutes and the patient should be closely watched until emergency help is received.” to include the amount of time to wait prior to administering an additional dose.

#### 4.2 RECOMMENDATIONS FOR ADAPT PHARMA, INC.

We recommend the Applicant implement the following prior to approval of this NDA. These changes to the user interface do not require an additional human factors validation study.

##### 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 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:<sup>1</sup>  
MMMYYYY (e.g., JAN2015) or MMMDDYYYY (e.g., JAN012015)
3. We recommend you change the font color of the strength from gray to black to increase its prominence.

---

<sup>1</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

## 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.



---

<sup>2</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

<sup>3</sup> Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3

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.<sup>5</sup>
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)  
” to “If the person does not respond (b) (4)

---

<sup>4</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

<sup>5</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

- (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.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Narcan (naloxone hydrochloride) nasal spray that Adapt Pharma, Inc. submitted on June 19, 2015.

Table 2. Relevant Product Information for Narcan (naloxone hydrochloride) nasal spray	
<b>Initial Approval Date</b>	Not Applicable
<b>Active Ingredient</b>	naloxone hydrochloride
<b>Indication</b>	Narcan nasal spray is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
<b>Route of Administration</b>	intranasal
<b>Dosage Form</b>	nasal spray
<b>Strength</b>	4 mg per 0.1 mL
<b>Dose and Frequency</b>	Administer a single spray of Narcan nasal spray to adults or pediatric patients nasally into one nostril
<b>How Supplied</b>	(b) (4) carton containing 2 Narcan nasal sprays
<b>Storage</b>	Store at controlled room temperature 15°C to 25°C (59°F to 77°F) excursions permitted between 4°C and 40°C (between 39°F and 104°F). Do not Freeze.
<b>Container Closure</b>	nasal spray actuator in a blister

## APPENDIX B. PREVIOUS DMEPA REVIEWS

### B.1 Methods

On July 20, 2015, we searched the L:drive and AIMS using the term, 114704 (IND associated with this NDA), to identify reviews previously performed by DMEPA.

### B.2 Results

Our search identified one previous human factors protocol review<sup>6</sup>, and we confirmed that our previous recommendations were implemented or considered.

Table 3. Summary of Previous DMEPA Reviews for Narcan (naloxone hydrochloride) nasal spray		
OSE RCM #	Review Date	Summary of Recommendations
2015-320	March 12, 2015	This review evaluated the human factors study protocol. We determined the human factors study protocol is adequate to support review of the proposed labeling. We provided recommendations for the Sponsor to address prior to submission of their pivotal human factors study.

---

<sup>6</sup> Calderon M. Human Factors Protocol Review for naloxone hydrochloride intranasal spray (IND 114704). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAR 12. 5 p. OSE RCM No.: 2015-320.

## APPENDIX C. HUMAN FACTORS STUDY (1 DEVICE, 4 MG)

### C.1 Study Design

Objectives	<p><u>Human Factors:</u> To evaluate the subject's ability to perform the 5 usage steps correctly from the IFU.</p> <p><u>Comprehension:</u> To evaluate the subject's ability to respond to the 9 key comprehension objectives correctly in the Patient Information section.</p>
Primary Objectives	<p><u>Human Factors:</u> Subjects correctly completed the critical tasks in the human factors simulated use:</p> <ol style="list-style-type: none"><li>1. Insert nozzle into nostril</li><li>2. Press plunger to release dose into nose</li></ol> <p>Performance of the tasks was coded as "correct" if it was performed according to the directions in the IFU</p> <p><u>Comprehension:</u> Subjects correctly responded to the following comprehension objectives from the Patient Information section:</p> <ol style="list-style-type: none"><li>1. After using TRADENAME NASAL for an overdose, is it still necessary to get emergency medical help?</li><li>2. How should TRADENAME NASAL be used?</li><li>3. What is TRADENAME NASAL?</li><li>4. What is one example of a sign of an opioid emergency?</li><li>5. What is TRADENAME NASAL used for?</li><li>6. Which of the following is a potential withdrawal symptom after someone receives TRADENAME NASAL?</li></ol>
Secondary Objectives	<p>Subjects correctly completed the secondary tasks in the human factors simulated use:</p> <ol style="list-style-type: none"><li>1. Check for response</li><li>2. Call 911</li><li>3. Move to Recovery Position after administering dose</li></ol>
Exploratory Objectives	<p>Exploratory objectives were obtained for information. Subjects correctly responded to the following comprehension objectives from the Patient Information section:</p> <ol style="list-style-type: none"><li>1. Who should not use this product?</li><li>2. Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL?</li><li>3. Will TRADENAME NASAL have any effect in people who are not taking opioid medicines?</li></ol>
Study Population	<p>Approximately 50 subjects representing the general population, ages 12 and older, were recruited for this study; 53 subjects completed the study. Two subgroups (low literacy and adolescents) were also recruited.</p>

	Participants	Number of Participants
	General participants, ages 12 and older	53
	Low literacy subgroup	16
	Adolescents (12-17 years of age) subgroup	16
Inclusion Criteria	<p>The following inclusion criteria applied to all participants:</p> <ol style="list-style-type: none"> <li>1. The subject was male or female, of any race.</li> <li>2. The subject was 12 years of age or older</li> <li>3. The subject must have been able to read, speak and understand English sufficiently to understand the nature of the study procedures.</li> <li>4. At the study site, the subject must have agreed to follow the specified instructions and procedures and must have voluntarily signed the CDA and the Informed Consent/Assent form. <ul style="list-style-type: none"> <li>○ If the subject was less than 18 years of age: a parent/guardian must have been present to sign the Consent/Assent form and give permission for adolescent to participate.</li> </ul> </li> </ol>	
Exclusion Criteria	<p>The following exclusion criteria applied to all participants:</p> <ol style="list-style-type: none"> <li>1. The subject had ever been trained or employed as a healthcare professional (physician, nurse, nurse practitioner, physician assistant, or pharmacist).</li> <li>2. The subject or anyone in their household currently worked for marketing, marketing consulting, or marketing research company, an advertising agency or public relations firm, a pharmaceutical company, a pharmacy, a managed care or health insurance company as a healthcare professional, a healthcare practice, or a public health agency such as Health and Human Services or the FDA.</li> <li>3. The subject had, or could not remember if he/she had, participated in any clinical trial, product label study or market research study in the past twelve (12) months.</li> <li>4. The subject normally wore corrective lenses, contacts or glasses to read and did not have them with them.</li> <li>5. The subject had any other impairment that would prevent him/her from being able to read on his/her own.</li> </ol>	
Methodology	<p>This was a multi-site, single-visit, Human Factors Validation Study, conducted among a general population of male and female subjects who were 12 years of age or older. Low literacy subjects were included in the study population.</p> <p>Upon arrival at the site, subjects reviewed and signed a Confidentiality/Non-Disclosure Agreement (CDA) and an Informed</p>	

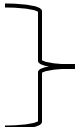


	<p>Consent/Assent Form prior to the start of the study. Parents of subjects 12-17 also signed the Informed Consent/Assent, giving permission for their adolescent to participate in the study.</p> <p>For literacy testing, adult subjects (ages 18+) completed the Rapid Estimate of Adult Literacy in Medicine (REALM) test; adolescent subjects completed the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) test.</p> <p>All subjects participated in a human factors demonstration of the product on a mannequin [similar to those used for cardiopulmonary (CPR) training]. This mannequin was intended to simulate an unconscious overdose victim. The simulated use testing was followed by a self-administered comprehension survey.</p> <p>Subjects completed the simulated use with no prior review of the IFU. Subjects were presented with a real-life scenario of an unconscious overdose victim. They were given the product and labeling and asked to proceed as they would in real-life. No training or coaching was given prior to or during the simulated use testing.</p> <p>A Trained Observer documented if the subject completed the following usage steps correctly or incorrectly:</p> <ul style="list-style-type: none"> <li>• Task 1a: Check for response (Secondary objective)</li> <li>• Task 2a: Insert nozzle into nostril (Primary objective)</li> <li>• Task 2b/2c: Press plunger to release dose into nose (Primary objective)</li> <li>• Task 3a: Call 911 (Secondary objective)</li> <li>• Task 3b: Move to Recovery Position after administering dose (Secondary objective)</li> </ul> <p>Environmental distractions were included in the room to mimic potential real-life situations:</p> <ul style="list-style-type: none"> <li>• Background distraction from common noises, such as TV and radio</li> <li>• A Trained Observer was in the room to observe the subject's actions; this person also simulated a bystander who might be observing during an emergency. However, there was no guidance, coaching, praise, or critique from the Observer.</li> </ul> <p>The subject was then taken to a separate room to complete the comprehension interview with a Trained Moderator. The Moderator gave the Patient Information portion of the Prescribing Information to</p>
--	--

	<p>the subject to review independently. Following his/her review, the subject completed a self-administered comprehension questionnaire, which contained multiple-choice questions - one for each objective. The Patient Information sheet remained available to the subject to refer to throughout the completion of the survey.</p> <p>Follow-up questions were asked to understand the reasons for any incorrect tasks or incorrect comprehension responses. After the follow-up interview, the subject was considered to have completed the study.</p>
--	--

## C.2 Results for General Population

### C.2.1 Critical Tasks

	General population (n=53)	
Both Critical Tasks	n (%)	(95% CI)
Insert nozzle into nostril <b>AND</b> Press plunger to release dose into nose (Location/Dose Released) 	48 (90.6)	(79.34, 96.87)

Success was determined based on correctly completing both critical tasks correctly. 90.6% (n=48 of 53) of subjects correctly performed both critical tasks.

### C.2.2 Secondary Tasks

	General population (n=53)	
Secondary Task	n (%)	(95% CI)
Check for a response	44 (83.0)	(70.20, 91.93)
Call 911	38 (71.7)	(57.65, 83.21)
Move to the recovery position	20 (37.7)	(24.79, 52.11)

### C.2.3 Primary Comprehension Objectives

	General population (n=53)	
Primary Comprehension Objective	n (%)	(95% CI)
After using TRADENAME NASAL for an overdose, is it still necessary to get emergency medical help?	53 (100.0)	(93.28, 100.00)
How should TRADENAME NASAL be used?	53 (100.0)	(93.28, 100.00)

What is TRADENAME NASAL?	51 (96.2)	(87.02, 99.54)
What is one example of a sign of an opioid emergency?	50 (94.3)	(84.34, 98.82)
What is TRADENAME NASAL used for?	46 (86.8)	(74.66, 94.52)
Which of the following is a potential withdrawal symptom after someone receives TRADENAME NASAL?	41 (77.4)	(63.79, 87.72)

### C.2.4 Exploratory Comprehension Objectives

	General population (n=53)	
Exploratory Comprehension Objective	n (%)	(95% CI)
Who should not use this product?	49 (92.5)	(81.79, 97.91)
Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL?	42 (79.2)	(65.89, 89.16)
Will TRADENAME NASAL have any effect in people who are not taking opioid medicines?	37 (69.8)	(55.66, 81.66)

## C.3 Results for Low Literacy Subgroup Population

### C.3.1 Critical Tasks

	Low Literacy (n=16)	Normal Literacy (n=37)
Both Critical Tasks	n (%)	n (%)
Insert nozzle into nostril <b>AND</b> Press plunger to release dose into nose (Location/Dose Released)	14 (87.5)	34 (91.9)

Results within the low literate population (87.5%, n=14 of 16) were similar to the normal literate population (91.9%, n=34 of 37) for their correct performance of both critical tasks.

### C.3.2 Secondary Tasks

	Low Literacy (n=16)	Normal Literacy (n=37)
Secondary Task	n (%)	n (%)
Check for a response	11 (68.8)	33 (89.2)
Call 911	12 (75.0)	26 (70.3)

Move to the recovery position	6 (37.5)	14 (37.8)
-------------------------------	----------	-----------

### C.3.3 Primary Comprehension Objectives

	Low Literacy (n=16)	Normal Literacy (n=37)
Primary Comprehension Objective	n (%)	n (%)
After using TRADENAME NASAL for an overdose, is it still necessary to get emergency medical help?	16 (100.0)	37 (100.0)
How should TRADENAME NASAL be used?	16 (100.0)	37 (100.0)
What is TRADENAME NASAL?	15 (93.8)	36 (97.3)
What is one example of a sign of an opioid emergency?	14 (87.5)	36 (97.3)
What is TRADENAME NASAL used for?	14 (87.5)	32 (86.5)
Which of the following is a potential withdrawal symptom after someone receives TRADENAME NASAL?	10 (62.5)	31 (83.8)

Results for the 6 primary comprehension objectives within the low literate population (62.5% - 100.0%) were lower than the normal literate population (83.8% - 100.0%). The lower score for low literacy subjects was due primarily to one communication objective related to “Withdrawal symptom after administering a dose (Vomiting)”.

### C.3.4 Exploratory Comprehension Objectives

	Low Literacy (n=16)	Normal Literacy (n=37)
Exploratory Comprehension Objective	n (%)	n (%)
Who should not use this product?	13 (81.3)	36 (97.3)
Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL?	10 (62.5)	32 (86.5)
Will TRADENAME NASAL have any effect in people who are not taking opioid medicines?	8 (50.0)	29 (78.4)

## C.4 Results for Adolescent Subgroup Population

### C.4.1 Critical Tasks

	Adolescent (n=16)	Adult (n=37)
Both Critical Tasks	n (%)	n (%)
Insert nozzle into nostril <b>AND</b> Press plunger to release dose into nose (Location/Dose Released)	13 (81.3)	35 (94.6)

Results for correct performance of both critical tasks within the adolescent population (81.3%, n=13 of 16) and the adult population (94.6%, n=35 of 37).

#### C.4.2 Secondary Tasks

	Adolescent (n=16)	Adult (n=37)
Secondary Task	n (%)	n (%)
Check for a response	13 (81.3)	31 (83.8)
Call 911	8 (50.0)	30 (81.1)
Move to the recovery position	5 (31.3)	15 (40.5)

#### C.4.3 Primary Comprehension Objectives

	Adolescent (n=16)	Adult (n=37)
Primary Comprehension Objective	n (%)	n (%)
After using TRADENAME NASAL for an overdose, is it still necessary to get emergency medical help?	16 (100.0)	37 (100.0)
How should TRADENAME NASAL be used?	16 (100.0)	37 (100.0)
What is TRADENAME NASAL?	16 (100.0)	35 (94.6)
What is one example of a sign of an opioid emergency?	15 (93.8)	35 (94.6)
What is TRADENAME NASAL used for?	12 (75.0)	34 (91.9)
Which of the following is a potential withdrawal symptom after someone receives TRADENAME NASAL?	14 (87.5)	27 (73.0)

Results for the primary comprehension objectives within the adolescent population (75.0% - 100.0%) were similar to the adult population (73.0% - 100.0%).

#### C.4.4 Exploratory Comprehension Objectives

	Adolescent (n=16)	Adult (n=37)
--	-------------------	--------------

Exploratory Comprehension Objective	n (%)	n (%)
Who should not use this product?	15 (93.8)	34 (91.9)
Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL?	13 (81.3)	29 (78.4)
Will TRADENAME NASAL have any effect in people who are not taking opioid medicines?	10 (62.5)	27 (73.0)

## C.5 Results-Areas of Difficulty and Areas for Improvement

After completing the simulated use of the device, all subjects were asked a set of open-ended questions for identifying any areas of confusion or difficulty when using the product; subjects were also asked for potential areas of improvement.

### C.5.1 Areas of Difficulty

No difficulty (52.8%; n=28)

The most common areas of difficulty were related to:

- Nozzle was too large for the mannequin's nostril/difficulty inserting into the nostril (n=5)
- Uncertainty about the number of doses/thought it contained 2 doses (n=5)
- Had trouble opening the package/didn't realize it could peel open (n=4)
- Plunger was difficult to operate/difficulty with pressure of plunger (n=4)

### C.5.2 Areas for Improvement

Approximately three-quarters of subjects (75.5%; n=40) did provide suggestions for improvement areas. The top mentioned areas of improvement included the following:

- Further simplify instructions/reduce # of steps (n=11)
- Pictures: increase size/improve/add more graphics/simplify/make words larger on pictures (n=9)
- Be more clear in how to place fingers on plunger (n=7)
- Make it easier to open (n=6)

## **APPENDIX F. HUMAN FACTORS STUDY (2 DEVICES, 2 MG EACH)**

The Sponsor also submitted a separate human factors validation study to evaluate the use of two nasal sprays, each containing 2 mg, to be administered 2 to 3 minutes apart. The design of the 2 nasal spray (2 mg each unit) study helped inform the design of the one nasal spray (4 mg) study. We sent an information request to the Sponsor to clarify the intent of the 2 nasal spray (2 mg each unit) study (see Appendix F). The Sponsor responded that they only plan to seek approval for the one nasal spray (4 mg) dosing regimen at this time. Therefore, we evaluated the 2 nasal spray (2 mg each unit study) in Appendix F.

### **F.1 Information Request from DMEPA and Response from Sponsor (dated July 15, 2015)**

#### **Information Request from DMEPA (dated July 15, 2015)**

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.

#### **Response from Sponsor (dated July 15, 2015)**

Adapt is providing the responses below to the Agency questions and comments:

1. The Human Factor studies were designed prior to the pre-NDA discussions with the Agency and a final decision of Adapt to pursue only the 4 mg IN dose of Narcan Nasal Spray. Given the timing of the submission, Adapt duplicated the studies with the two options (1 device of 4 mg and 2 devices of 2 mg) based on the formulation development and completed pharmacokinetics studies. Adapt currently only plans on filing the 4 mg IN dose and launching this as an optimal dose for out of hospital use.
  - a. The intent of the first Human Factor study (2 x 2 mg IN doses) was to evaluate this option in an out of hospital setting. In fact, while some instructions were followed well in our simulated testing, in the 2 x 2 mg IN study, the steps to administer the first dose were well followed. However, when the subjects were supposed to evaluate the patient status for 2-3 minutes and then determine if a 2nd dose was needed, in many cases the subject did not wait and just administered the second dose almost immediately. The repeat dose and evaluation of the patient status prior to dosing were problematic with the test groups. In a large percentage of the test group, subjects did not wait to evaluate the patient and generally dosed twice regardless of the patients response. While the two dose (2 x 2 mg IN doses) is

certainly still an option, this scenario was considered less attractive for an out of hospital emergency situation. As such, Adapt decided that a single 4 mg IN dose that approximates the widely used 2 mg IM dose in the hospital setting, was the most appropriate dose for emergency at home administration. We are happy to discuss this further with the agency during the review, if needed.

b. See above. At this time, Adapt only intends on marketing the 4 mg IN dose.

2. The final Quick Start Guide is attached. This will be included in the final submission as part of the labeling. We note that the Quick Start Guide used for each of the above Human Factor studies is included in the report:

2 x 2 mg Study: Page 109 of 734

2 mg study: page 100 of 442

Finally, the Risk Assessment is referenced in both reports and is contained in the following:

2 x 2 mg Study: Page 32 of 734

4 mg Study: Page 29 of 442.

## F.2 Study Design

Objectives	<p><u>Human Factors:</u> To evaluate the subject's ability to perform the 5 usage steps correctly from the IFU.</p> <p><u>Comprehension:</u> To evaluate the subject's ability to respond to the 9 key comprehension objectives correctly in the Patient Information section.</p>
Primary Objectives	<p><u>Human Factors:</u> Subjects correctly completed the critical tasks in the human factors simulated use:</p> <ol style="list-style-type: none"> <li>1. Insert nozzle into nostril</li> <li>2. Press plunger to release dose into nose</li> </ol> <p>Performance of the tasks was coded as "correct" if it was performed according to the directions in the IFU</p> <p><u>Comprehension:</u> Subjects correctly responded to the following comprehension objectives from the Patient Information section:</p> <ol style="list-style-type: none"> <li>1. After using TRADENAME NASAL for an overdose, is it still necessary to get emergency medical help?</li> <li>2. How should TRADENAME NASAL be used?</li> <li>3. What is TRADENAME NASAL?</li> <li>4. What is one example of a sign of an opioid emergency?</li> <li>5. What is TRADENAME NASAL used for?</li> <li>6. Which of the following is a potential withdrawal symptom after</li> </ol>



	someone receives TRADENAME NASAL? 7. How should TRADENAME NASAL be used?															
Secondary Objectives	Subjects correctly completed the secondary tasks in the human factors simulated use: 1. Check for response 2. Call 911 3. Move to Recovery Position after administering dose 4. Wait 2-3 minutes and assess effectiveness of first dose 5. Re-administer using a new unit (if needed)															
Exploratory Objectives	Exploratory objectives were obtained for information. Subjects correctly responded to the following comprehension objectives from the Patient Information section: 1. Who should not use this product? 2. Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL? 3. Will TRADENAME NASAL have any effect in people who are not taking opioid medicines?															
Study Population	Approximately 60 subjects representing the general population, ages 12 and older, were recruited for this study; 63 subjects completed the study. Two subgroups (low literacy and adolescents) were also recruited.  Upon arrival at the site, subjects were randomized to one of two study arms:  <u>Arm 1 (n=32):</u> Subjects were given the Quick Start Guide (QSG) to review independently in advance of completing the demonstration  <u>Arm 2 (n=31):</u> Subjects were taken directly to the demonstration and given the OSG and product without advance review of the information. <table><tr><td></td><td>Arm 1</td><td>Arm 2</td></tr><tr><td>Participants</td><td>n (%)</td><td>n (%)</td></tr><tr><td>General participants, ages 12 and older</td><td>32 (51%)</td><td>31 (49%)</td></tr><tr><td>Low literacy subgroup</td><td>10 (31%)</td><td>10 (32%)</td></tr><tr><td>Adolescents (12-17 years of age) subgroup</td><td>8 (25%)</td><td>9 (29%)</td></tr></table>		Arm 1	Arm 2	Participants	n (%)	n (%)	General participants, ages 12 and older	32 (51%)	31 (49%)	Low literacy subgroup	10 (31%)	10 (32%)	Adolescents (12-17 years of age) subgroup	8 (25%)	9 (29%)
	Arm 1	Arm 2														
Participants	n (%)	n (%)														
General participants, ages 12 and older	32 (51%)	31 (49%)														
Low literacy subgroup	10 (31%)	10 (32%)														
Adolescents (12-17 years of age) subgroup	8 (25%)	9 (29%)														
Inclusion Criteria	The following inclusion criteria applied to all participants: <ul style="list-style-type: none"><li>• The subject was male or female, of any race.</li><li>• The subject was 12 years of age or older</li><li>• The subject must have been able to read, speak, and understand English sufficiently to understand the nature of the study</li></ul>															

	<p>procedures.</p> <ul style="list-style-type: none"> <li>At the study site, the subject must have agreed to follow the specified instructions and procedures and must have voluntarily signed the CDA and the Informed Consent/Assent form. <ul style="list-style-type: none"> <li>If the subject was less than 18 years of age, a parent/guardian must have been present to sign the Consent/Assent form and give permission for adolescent to participate.</li> </ul> </li> </ul>
Exclusion Criteria	<p>The following exclusion criteria applied to all participants:</p> <ul style="list-style-type: none"> <li>The subject had ever been trained or employed as a healthcare professional (physician, nurse, nurse practitioner, physician assistant, or pharmacist).</li> <li>The subject or anyone in their household currently worked for marketing, marketing consulting, or marketing research company, an advertising agency or public relations firm, a pharmaceutical company, a pharmacy, a managed care or health insurance company as a healthcare professional, a healthcare practice, or a public health agency such as Health and Human Services or the FDA.</li> <li>The subject had, or could not remember if he/she had, participated in any clinical trial, product label study or market research study in the past twelve (12) months.</li> <li>The subject normally wore corrective lenses, contacts, or glasses to read and did not have them with them.</li> <li>The subject had any other impairment that would prevent him/her from being able to read on his/her own.</li> </ul>
Methodology	<p>This was a multi-site, single-visit, Human Factors Validation Study, conducted among a general population of male and female subjects who were 12 years of age or older. Low literacy subjects were included in the study population.</p> <p>Upon arrival at the site, subjects reviewed and signed a Confidentiality/Non-Disclosure Agreement (CDA) and an Informed Consent/Assent Form prior to the start of the study. Parents of subjects 12-17 also signed the Informed Consent/Assent, giving permission for their adolescent to participate in the study.</p> <p>For literacy testing, adult subjects (ages 18+) completed the Rapid Estimate of Adult Literacy in Medicine (REALM) test; adolescent subjects completed the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) test.</p> <p>All subjects participated in a human factors demonstration of the</p>

	<p>product on a mannequin [similar to those used for cardiopulmonary (CPR) training]. This mannequin was intended to simulate an unconscious overdose victim. The simulated use testing was followed by a self-administered comprehension survey.</p> <ul style="list-style-type: none"> <li>• Subjects were randomized into one of two study arms (Arm 1- Review QSG in advance or Arm 2- Do not review QSG in advance)</li> <li>• The subject was given a brief overview of the study <ul style="list-style-type: none"> <li>○ Arm 1 subjects were given the QSG to review independently at this time</li> </ul> </li> <li>• The subject was then escorted to a demonstration room with a one-way mirror for observation</li> <li>• Prior to entering the room, the subjects were presented with a real-life scenario of an unconscious overdose victim. The subject was told that a carton containing TRADENAME NASAL and instructions for use will be on a table in the room</li> </ul> <p>A Trained Observer documented if the subject completed the following usage steps correctly or incorrectly:</p> <ul style="list-style-type: none"> <li>• Task 1a: Check for response (Secondary objective)</li> <li>• Task 2a: Insert nozzle into nostril (Primary objective)</li> <li>• Task 2b/2c: Press plunger to release dose into nose (Primary objective)</li> <li>• Task 3a: Call 911 (Secondary objective)</li> <li>• Task 3b: Move to Recovery Position after administering dose (Secondary objective)</li> <li>• Task 4a: Wait 2 to 3 minutes and assess effectiveness of first dose (Secondary objective)</li> <li>• Task 4c: Re-administer using a new unit (if needed) (Secondary objective)</li> </ul> <p>Environmental distractions were included in the room to mimic potential real-life situations:</p> <ul style="list-style-type: none"> <li>• Background distraction from common noises, such as TV and radio</li> <li>• A Trained Observer was in the room to observe the subject's actions; this person also simulated a bystander who might be observing during an emergency. However, there was no guidance, coaching, praise, or critique from the Observer.</li> </ul> <p>The subject was then taken to a separate room to complete the comprehension interview with a Trained Moderator. The Moderator gave the Patient Information portion of the Prescribing Information to the subject to review independently. Following his/her review, the</p>
--	---

	<p>subject completed a self-administered comprehension questionnaire, which contained multiple-choice questions - one for each objective. The Patient Information sheet remained available to the subject to refer to throughout the completion of the survey.</p> <p>Follow-up questions were asked to understand the reasons for any incorrect tasks or incorrect comprehension responses. After the follow-up interview, the subject was considered to have completed the study.</p>
--	---

## F.2 Results for General Population

### F.2.1 Critical Tasks

	Arm 1 (n=32)		Arm 2 (n=31)	
Both Critical Tasks	n (%)	(95% CI)	n (%)	(95% CI)
Insert nozzle into nostril <b>AND</b> Press plunger to release dose into nose (Location/Dose Released)	29 (90.6)	(74.98, 98.02)	28 (90.3)	(74.25, 97.96)

Success was determined by completing both critical tasks.

### F.2.2 Secondary Tasks

	Arm 1 (n=32)		Arm 2 (n=31)	
Secondary Task	n (%)	(95% CI)	n (%)	(95% CI)
Check for a response	30 (93.8)	(79.19, 99.23)	24 (77.4)	(58.90, 90.41)
Call 911	24 (75.0)	(56.60, 88.54)	25 (80.6)	(62.53, 92.55)
Move to the recovery position	22 (68.8)	(49.99, 83.88)	15 (48.4)	(30.15, 66.94)
Wait 2 to 3 minutes and assess effectiveness of first dose	19 (59.4)	(40.64, 76.30)	17 (54.8)	(36.03, 72.68)
Re-administer using a new unit (if needed)	24 (80.0)	(61.43, 92.29)	21 (70.0)	(50.60, 85.27)

The majority of subjects demonstrated a correct action for Check for a response, Call 911, and Re-administer using a new unit (if needed).

### F.2.3 Primary Comprehension Objectives

	General Population (n=63)	
Primary Comprehension Objective	n (%)	(95% CI)
After using TRADENAME NASAL for an overdose, is it still necessary to get emergency medical help?	62 (98.4)	(91.47, 99.96)
How should TRADENAME NASAL be used?	60 (95.2)	(86.71, 99.01)
What is TRADENAME NASAL?	63 (100.0)	(94.31, 100.0)
What is one example of a sign of an opioid emergency?	57 (90.5)	(80.41, 96.42)
What is TRADENAME NASAL used for?	54 (85.7)	(74.61, 93.25)
Which of the following is a potential withdrawal symptom after someone receives TRADENAME NASAL?	55 (87.3)	(76.50, 94.35)

All six primary comprehension objectives scored 85% or higher.

#### F.2.4 Exploratory Comprehension Objectives

	General population (n=63)	
Exploratory Comprehension Objective	n (%)	(95% CI)
Who should not use this product?	58 (92.1)	(82.44, 97.37)
Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL?	55 (87.3)	(76.50, 94.35)
Will TRADENAME NASAL have any effect in people who are not taking opioid medicines?	50 (79.4)	(67.30, 88.53)

Two exploratory comprehension objectives scored 87% or higher.

### F.3 Results for Low Literacy Subgroup Population

#### F.3.1 Critical Tasks

	Arm 1		Arm 2	
	Low Literacy (n=10)	Normal Literacy (n=22)	Low Literacy (n=10)	Normal Literacy (n=21)
Both Critical Tasks	n (%)	n (%)	n (%)	n (%)

Insert nozzle into nostril <b>AND</b> Press plunger to release dose into nose (Location/Dose Released)	8 (80.0)	21 (95.5)	8 (80.0)	20 (95.2)
---	----------	-----------	----------	-----------

Results for the low literacy subgroup population were lower for correct completion of both critical tasks compared to the normal literacy population in both study arms.

### F.3.2 Secondary Tasks

	Arm 1		Arm 2	
	Low Literacy (n=10)	Normal Literacy (n=22)	Low Literacy (n=10)	Normal Literacy (n=22)
Secondary Task	n (%)	n (%)	n (%)	n (%)
Check for a response	8 (80.0)	22 (100.0)	7 (70.0)	17 (81.0)
Call 911	6 (60.0)	18 (81.8)	7 (70.0)	18 (85.7)
Move to the recovery position	7 (70.0)	15 (68.2)	2 (20.0)	13 (61.9)
Wait 2 to 3 minutes and assess effectiveness of first dose	3 (30.0)	16 (72.7)	3 (30.0)	14 (66.7)
Re-administer using a new unit (if needed)	5 (50.0)* *n=10	19 (95.0)* *n=20	7 (70.0)* *n=10	14 (70.0)* *n=20

### F.3.3 Primary Comprehension Objectives

	Low Literacy (n=20)	Normal Literacy (n=43)
Primary Comprehension Objective	n (%)	n (%)
After using TRADENAME NASAL for an overdose, is it still necessary to get emergency medical help?	20 (100.0)	42 (97.7)
How should TRADENAME NASAL be used?	18 (90.0)	42 (97.7)
What is TRADENAME NASAL?	20 (100.0)	43 (100.0)
What is one example of a sign of an opioid emergency?	15 (75.0)	42 (97.7)
What is TRADENAME NASAL used for?	14 (70.0)	40 (93.0)
Which of the following is a potential withdrawal symptom after someone receives TRADENAME NASAL?	15 (75.0)	40 (93.0)

Results for the correct response to the six primary comprehension objectives were lower for the low literacy subgroup population than for the normal literacy population.

### F.3.4 Exploratory Comprehension Objectives

	Low Literacy (n=20)	Normal Literacy (n=43)
Exploratory Comprehension Objective	n (%)	n (%)
Who should not use this product?	17 (85.0)	41 (95.3)
Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL?	15 (75.0)	40 (93.0)
Will TRADENAME NASAL have any effect in people who are not taking opioid medicines?	15 (75.0)	35 (81.4)

## F.4 Results for Adolescent Subgroup Population

### F.4.1 Critical Tasks

	Arm 1		Arm 2	
	Adolescent (n=8)	Adult (n=24)	Adolescent (n=9)	Adult (n=22)
Both Critical Tasks	n (%)	n (%)	n (%)	n (%)
Insert nozzle into nostril <b>AND</b> Press plunger to release dose into nose (Location/Dose Released)	6 (75.0)	23 (95.8)	8 (88.9)	20 (90.9)

Results for the adolescent subgroup population were lower for correct completion of both critical tasks compared to the normal literacy population in arm 1 and similar in arm 2.

### F.4.2 Secondary Tasks

	Arm 1		Arm 2	
	Adolescent (n=8)	Adult (n=24)	Adolescent (n=9)	Adult (n=22)
Secondary Task	n (%)	n (%)	n (%)	n (%)
Check for a response	7 (87.5)	23 (95.8)	6 (66.7)	18 (81.8)
Call 911	2 (25.0)	22 (91.7)	5 (55.6)	20 (90.9)
Move to the recovery position	7 (87.5)	15 (62.5)	2 (22.2)	13 (59.1)

Wait 2 to 3 minutes and assess effectiveness of first dose	5 (62.5)	14 (58.3)	3 (33.3)	14 (63.6)
Re-administer using a new unit (if needed)	6 (75.0)* *n=8	18 (81.8)* *n=22	6 (75.0)* *n=8	15 (68.2)* *n=22

### F.4.3 Primary Comprehension Objectives

	Adolescent (n=17)	Adult (n=46)
Primary Comprehension Objective	n (%)	n (%)
After using TRADENAME NASAL for an overdose, is it still necessary to get emergency medical help?	16 (94.1)	46 (100.0)
How should TRADENAME NASAL be used?	15 (88.2)	45 (97.8)
What is TRADENAME NASAL?	17 (100.0)	46 (100.0)
What is one example of a sign of an opioid emergency?	15 (88.2)	42 (91.3)
What is TRADENAME NASAL used for?	15 (88.2)	39 (84.8)
Which of the following is a potential withdrawal symptom after someone receives TRADENAME NASAL?	14 (82.4)	41 (89.1)

Results for the correct response for the six primary comprehension objectives were similar for the adolescent subgroup population and the adult population.

### F.4.4 Exploratory Comprehension Objectives

	Adolescent (n=17)	Adult (n=46)
Exploratory Comprehension Objective	n (%)	n (%)
Who should not use this product?	15 (88.2)	43 (93.5)
Which of the following is an example of something you should tell your healthcare provider before using TRADENAME NASAL?	13 (76.5)	42 (91.3)
Will TRADENAME NASAL have any effect in people who are not taking opioid medicines?	14 (82.4)	36 (78.3)

### F.5 Results-Areas of Difficulty and Areas for Improvement

After completing the simulated use of the device, all subjects were asked a set of open-ended questions for identifying any areas of confusion or difficulty when using the product; subjects were also asked for potential areas of improvement.



### F.5.1 Areas of Difficulty

No difficulty (n=26, 41.3%)

The most common areas of difficulty were related to:

- Had trouble opening the package/didn't realize it could peel open (n=13)
- Nozzle was too large for the mannequin's nostril/difficulty inserting into the nostril (n=6)
- Uncertainty if supposed to use two doses/when to use second dose (n=6)
- Placement of hands/fingers was confusing (n=4)
- Package insert was confusing/too much to read in an emergency (n=4)

### F.5.2 Areas for Improvement

Approximately three-quarters of subjects (n=46, 73%) provided suggestions for improvement.

The top areas for improvement were:

- Improve packaging/difficult to open/make it easier to open (n=16)
- Fonts, bold, color, larger, underline (n=7)

## F.6 Human Factors Study Assessment

### Critical Tasks

In Arm 1 (Review QSG in advance), 90.6% (n=29 of 32) of general participants were able to correctly complete both critical tasks. Similarly, in Arm 2 (Do not review QSG in advance), 90.3% (n=28 of 31) of general participants were able to correctly complete both critical tasks.

Six participants were unable to complete both critical tasks correctly. Four participants (2 participants in Arm 1 and 2 participants in Arm 2) did not press the plunger firmly enough to release the dose. All of these participants attempted to administer the dose in the nostril, but either did not press the plunger firmly enough, or pressed their fingers within the arms of the device and not the plunger itself. Our review of the carton labeling and IFU determined that the directions and picture associated with this step are clear. Therefore, we do not have further recommendations to mitigate the risk of these errors.

Two participants (1 participant in Arm 1 and 1 participant in Arm 2) released the dose in the air prior to administering it. One subject released the dose while testing the device while reading the QSG. The other subject appeared to have released the dose while aggressively attempting to open the packaging. Our review of the carton labeling and IFU determined that this step is clearly stated, including the statement, "Do not remove or test device before use." Therefore, we do not believe further changes to the user interface are likely to mitigate the risk for these errors.

### Secondary Tasks

For the secondary task of *Check for a response*, in Arm 1 (Review QSG in advance), 93.8% (n=30 of 32) of general participants correctly completed this task. In Arm 2 (Do not review QSG in

advance), 77.4% (n=24 of 31) of general participants correctly completed this task. Participants who were able to review the QSG in advance of the demonstration scored directionally higher on this task than those who did not. The most common reasons for not checking for a response were that subjects made an assumption that he had overdosed based on the scenario they were given or because he was on the floor, or subjects were focused on delivering the medication as quickly as possible due to the emergency situation. Our review of the carton labeling and IFU associated with this task determined that it is clearly labeled. Thus, we do not have further recommendations to mitigate the risk for these errors.

For the secondary task of *Call 911*, in Arm 1 (Review QSG in advance), 75% (n=24 of 32) of general participants correctly completed this task. In Arm 2 (Do not review QSG in advance), 80.6% (n=25 of 31) of general participants correctly completed this task. Scores for this task were similar regardless of whether participants reviewed the QSG prior to the demonstration. The most common rationale given by participants who did not make any attempt to call 911 was that they weren't certain if they were supposed to use the phone, due to the fact that this was a demonstration. Several subjects also mentioned they would have expected this direction to be one of the first, before administering the medicine. However, we believe that this direction is appropriately located in the IFU since administering the dose before calling 911 may be more beneficial to the patient so the medication can start taking effect.

For the secondary task of *Move to Recovery Position*, in Arm 1 (Review QSG in advance), 68.8% (n=22 of 32) of general participants correctly completed this task. In Arm 2 (Do not review QSG in advance), 48.4% (n=15 of 31) of general participants correctly completed this task. Participants who reviewed the QSG prior to the demonstration were more likely to complete this task correctly than those who did not. The most common reason for not completing this step was that participants saw the information but forgot it due to the other steps required, or participants made a conscious decision to leave the patient on his back due to concern with causing more harm, or they felt it was a better position for medical help. Additionally, several participants indicated the instructions were unclear. Our review of the carton labeling and IFU determined that Step 3 includes a picture of the recovery position; however, does not include a caption for the picture. Therefore, we recommend adding the statement, "Recovery Position" under the picture.

For the secondary task of *Wait 2 to 3 minutes to assess effectiveness of the first dose*, in Arm 1 (Review QSG in advance), 59.4% (n=19 of 32) of general participants correctly completed this task. In Arm 2 (Do not review QSG in advance), 54.8% (n=17 of 31) of general participants correctly completed this task. Most participants indicated that they were aware that every minute counted in the emergency and focused on trying to help the patient as quickly as possible. Participants also indicated that the information did not stand out and provided suggestions to improve the QSG. As the Sponsor is not currently pursuing approval of the 2 device 2 mg nasal spray dosing regimen (see response to information request in Section F.1) and this step is not included in the labeling materials submitted by the Sponsor on June 19, 2015, we do not have recommendations to mitigate the risk for these errors at this time.

For the secondary task of *Re-administer using a new unit*, in Arm 1 (Review QSG in advance), 80% (n=24 of 30) of general participants correctly completed this task. In Arm 2 (Do not review QSG in advance), 70% (n=21 of 30) of general participants correctly completed this task. The root cause of these errors was not reviewing the QSG or hurrying in an emergency, which caused the participants to miss this information. Participants also provided suggestions to improve the QSG. As the Sponsor is not currently pursuing approval of the 2 device 2 mg nasal spray dosing regimen (see response to information request in Section F.1) and this step is not included in the labeling materials submitted by the Sponsor on June 19, 2015, we do not have recommendations to mitigate the risk for these errors at this time.

#### Comprehension

The study protocol evaluated six primary comprehension objectives. All six primary comprehension objectives scored 85% or higher. The study protocol evaluated 3 exploratory comprehension objectives. Two of the exploratory comprehension objectives scored 87% or higher. For the question, *Will TRADENAME NASAL have any effect in people who are not taking opioid medicines*, 79.4% of participants answered correctly. Some participants indicated they could not find or did not see this information in the *Patient Information* section. Some participants misunderstood the question and assumed it would have some effect or cause some effect if someone were to use the medication regardless of the type of overdose. Our review of the *Patient Information* section determined that this information is presented clearly. Thus, we do not have recommendations for the *Patient Information* section of the prescribing information.

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

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

/s/  
-----

MILLIE C BRAHMBHATT  
09/03/2015

BRENDA V BORDERS-HEMPHILL  
09/03/2015

IRENE Z CHAN  
09/03/2015

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

**PATIENT LABELING REVIEW**

Date: August 25, 2015

To: Todd Bridges, RPh  
Director  
**Division of Medication Error Prevention and Analysis  
(DMEPA)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Nathan Caulk, MS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Review of Patient Labeling: Instructions for Use (IFU) and  
Quick Start Guide (QSG)

Drug Name (established name): NARCAN (naloxone hydrochloride)

Dosage Form and Route: nasal spray, 4 mg

Application Type/Number: NDA 208411

Applicant: Adapt Pharma Operations Limited

## **1 INTRODUCTION**

On July 20, 2015, Adapt Pharma Operations Limited submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 208411 for NARCAN (naloxone hydrochloride) nasal spray. On August 3, 2015, the Division of Medication Error Prevention and Analysis (DMEPA) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Instructions for Use (IFU) and Quick Start Guide (QSG) for NARCAN (naloxone hydrochloride) nasal spray.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by DMEPA to review the IFU and QSG that accompanies the packaging for the product.

## **2 MATERIAL REVIEWED**

- Draft NARCAN (naloxone hydrochloride) nasal spray IFU received on July 20, 2015, and received by DMPP on August 3, 2015.
- Draft NARCAN (naloxone hydrochloride) nasal spray QSG received on August 11, 2015.

## **3 REVIEW METHODS**

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

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

In our review of the IFU and QSG we have:

- simplified wording and clarified concepts where possible
- removed unnecessary or redundant information
- ensured that the IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## **4 CONCLUSIONS**

The IFU and QSG are acceptable with our recommended changes.

## **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the IFU and QSG is appended to this memorandum. Consult DMPP after the Applicant submits revised IFU and QSG to determine if additional revisions need to be made. Additional revisions to the IFU and QSG may be required during the NDA phase for consistency with the proposed Prescribing Information.

Please let us know if you have any questions.

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

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

/s/  
-----

NATHAN P CAULK

08/25/2015

LASHAWN M GRIFFITHS

08/25/2015