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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product: NARCAN nasal spray
Indication: Treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Applicant: Adapt Pharma Operations Limited
Review Division: Division of Anesthesia, Analgesia, and Addiction Products
Reviewer: Newton H. Woo, PhD
Supervisor: R. Daniel Mellon, PhD
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1 Executive Summary

1.1 Introduction

The Applicant, Adapt Pharmaceuticals, has submitted a 505(b)(2) NDA for an intranasal naloxone hydrochloride spray for the treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression with the intention of being used by laypersons or caregivers in the out-of-hospital, non-healthcare setting. This application is relying upon the published literature to support the safety and efficacy of this intranasal product. The Applicant owns the original NDA for Narcan (naloxone hydrochloride) injection.

1.2 Brief Discussion of Nonclinical Findings

The Applicant did not submit any new nonclinical studies to support this marketing NDA as none were required. Local tolerance studies would normally be required to support a reformulated drug product that employs an alternate route, however, the Division determined that nonclinical studies would not be required given the clinical experience with intranasal naloxone, lack of any novel excipients, the acute use of the drug product, and the potentially life-saving indication.

The Applicant has provided adequate data to support the safety of the drug substance, drug product, and drug product formulation. To support the safety of the container closure system, the Applicant has submitted extractables data under various extraction conditions. Under the most relevant solvent condition using water, no peaks were present indicating that there were no compounds that appeared after harsh extraction conditions. It is notable that a leachables assessment was not conducted but the Applicant has indicated that potential leachables will be evaluated in long-term stability samples. It is in the opinion of this Reviewer that the absence of leachables data does not preclude marketing approval for the following reasons: 1) the (b) (4) plungers is used in other FDA-approved aqueous based nasal and injectable drug products; 2) analysis of water extracts did not identify any substances; 3) the Applicant has committed to monitor for leachables during stability; 4) most importantly, this product is indicated for an acute, single-use indication; and 5) the drug product is a potentially life-saving therapy. The Applicant has committed to monitoring batches on stability for leachables. This should be solidified as a formal post-marketing commitment (PMC).

1.3 Recommendations

1.3.1 Approvability

From a pharmacology toxicology perspective, NDA 208411 may be approved with a post-marketing commitment (PMC).

1.3.2 Additional Non Clinical Recommendations

The following nonclinical study is recommended as a post-marketing commitment (PMC) should this NDA be approved in the first cycle:

As proposed, conduct and submit an adequate leachable safety assessment for your drug product and container closure system. This assessment must include leachable data from long-term stability studies taking into consideration the proposed shelf-life to determine if the specified extractables also leach into the drug product over time, and 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.

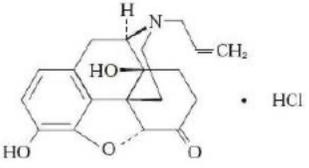
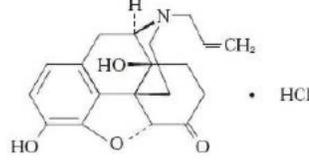
Additional Comments for the Leachables Assessment

- The leachable compounds you propose to evaluate in your leachables assessment appear appropriate.
- In your leachables assessment, evaluate at least three batches of your drug product over the course of your stability studies at multiple timepoints during the proposed shelf-life of your 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 this 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 that include any intended secondary container closure system(s) unless otherwise justified.
 - Published literature to support the safety of a leachable rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your container closure system.
 - Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the leachable.

1.3.3 Labeling

The following changes to the Applicant's proposed labeling are recommended in the table below. Refer to the action letter for final drug product labeling.

Applicant's Proposed labeling	Reviewer's proposed changes	Rationale for changes
<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy</p> <p><u>Risk Summary</u></p> <p>The (b) (4) available (b) (4) use (b) (4) in (b) (4) pregnant women to inform a drug-associated risk. In animal reproduction studies (b) (4) effects (b) (4) in mice and rats at doses (b) (4) -times, respectively (b) (4) dose of (b) (4) mg/day (b) (4) [see Data].</p> <p>(b) (4)</p> <p>the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.</p>	<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy</p> <p><u>Risk Summary</u></p> <p>The (b) (4) available (b) (4) use (b) (4) in (b) (4) pregnant women to inform a drug-associated risk. In animal reproduction studies (b) (4) no embryotoxic or teratogenic effects (b) (4) were observed in mice and rats treated with naloxone hydrochloride during the period of organogenesis at doses equivalent to (b) (4) 12-times, respectively, (b) (4) a human dose of (b) (4) 8 mg/day (two NARCAN nasal sprays) (b) (4) based on body surface area comparison. (b) (4) [see Data].</p> <p>(b) (4)</p> <p>the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.</p>	<p>Defer to Maternal Health Team.</p> <p>Changes were made to maintain consistency with other emergency use naloxone drug products and also update margins with a human dose of 8 mg/day (two NARCAN nasal sprays) based on body surface area and a 60 kg human.</p> <p>Defer to Maternal Health Team.</p>
<p><u>Data</u></p> <p>(b) (4)</p>	<p><u>Data</u></p> <p>(b) (4)</p>	<p>Defer to Maternal Health Team.</p>

(b) (4)		
<p>Animal Data Naloxone hydrochloride was administered during organogenesis to mice and rats at doses (b) (4) times, respectively, (b) (4) dose of (b) (4) mg/day (b) (4) based on body surface area (b) (4)). These (b) (4) studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride (b) (4)</p>	<p>Animal Data Naloxone hydrochloride was administered during organogenesis to mice and rats at subcutaneous doses up to 10 mg/kg/day (equivalent to (b) (4) 12-times, respectively, (b) (4) a human dose of (b) (4) 8 mg/day (two NARCAN nasal sprays) (b) (4) based on body surface area (b) (4) comparison). These (b) (4) studies demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride (b) (4)</p> <p>Pregnant female rats were administered 2 or 10 mg/kg naloxone subcutaneously from Gestation Day 15 to Postnatal day 21. There were no adverse effects on the offspring (up to 12-times a human dose of 8 mg/day (two NARCAN nasal sprays) based on body surface area comparison).</p>	<p>No significant changes recommended. The data are from the original NARCAN labeling. HED were based on a human dose of 8 mg/day (two NARCAN intranasal sprays) and 60 kg human.</p>
<p>11 DESCRIPTION</p> <p>NARCAN (naloxone hydrochloride) nasal spray is a pre-filled, single dose intranasal spray. (b) (4)</p> <p>Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:</p> <div style="text-align: center;">  <p><chem>C19H21NO4.HCl</chem> M.W. 363.84</p> </div> <p>Naloxone hydrochloride occurs as a white to slightly off-white</p>	<p>11 DESCRIPTION</p> <p>NARCAN (naloxone hydrochloride) nasal spray is a pre-filled, single dose intranasal spray. NARCAN does not contain any natural rubber latex. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:</p> <div style="text-align: center;">  <p><chem>C19H21NO4.HCl</chem> M.W. 363.84</p> </div> <p>Naloxone hydrochloride, an opioid antagonist, occurs as a white to</p>	

<p>powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.</p>	<p>slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.</p>	<p>The established pharmacological class should be included in this section.</p>
<p>12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action</p> <p>Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. (b) (4) it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.</p>	<p>12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action</p> <p>Naloxone hydrochloride is an opioid antagonist that antagonizes opioid effects by competing for the same receptor sites. Naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension (b) (4) it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.</p>	<p>No changes recommended.</p>
<p>13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><u>Carcinogenesis</u> Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.</p> <p><u>Mutagenesis</u> 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.</p> <p><u>Impairment of Fertility</u> (b) (4)</p>	<p>13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><u>Carcinogenesis</u> Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.</p> <p><u>Mutagenesis</u> 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.</p> <p><u>Impairment of Fertility</u> (b) (4)</p> <p>Male rats were treated with 2 or 10 mg/kg naloxone for 60 days prior to mating. Female rats treated for 14-days prior to mating and throughout gestation with the same doses of naloxone (up to 12-times a human dose of 8 mg/day (two NARCAN nasal sprays) based on body surface area comparison). There was no adverse effect on fertility.</p>	<p>No changes recommended.</p> <p>No changes recommended.</p> <p>(b) (4)</p> <p>HED were based on a human dose of 8 mg/day (two NARCAN intranasal sprays) and 60 kg human.</p>

2 Drug Information

2.1 Drug

CAS Registry Number
51481-60-8

Generic Name
Naloxone hydrochloride

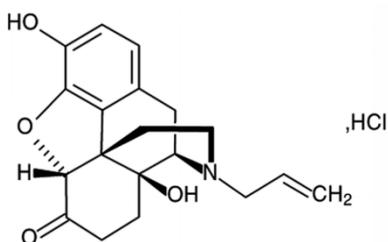
Code Name
N/A

Chemical Name
Morphinan-6-one,4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-,hydrochloride,(5 -),
dihydrate 17-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride
dihydrate

Molecular Formula/Molecular Weight

$C_{19}H_{21}NO_4 \cdot HCl$ (b) (4)

Structure



Pharmacologic Class

Opioid antagonist (Established Pharmacological Class)

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA	Drug Name	Division	Strength (route)	Marketing Status	AP Date	Indication	Sponsor
16636	Narcan (Naloxone HCl) Injection	DAAAP	1 mg/mL (IV, IM, SC)	Withdrawn FR Effective	August 20, 2010	The complete and partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids and diagnosis of suspected or known acute opioid overdose.	Adapt Pharma (formerly Endo)

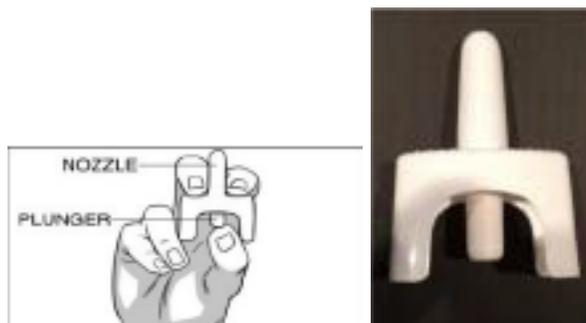
IND	Drug Name	Division	Status	Indication	Sponsor
114704	Naloxone HCl Nasal Spray	DAAAP	Active	For the complete or partial reversal of opioid depression, including respiratory depression induced by natural and synthetic opioids	Adapt Pharma

<i>DMF</i>	<i>Subject of DMF</i>	<i>Holder</i>	<i>Status and Submit Date</i>	<i>Reviewer's Comment</i>
		(b) (4)	Active since January 25, 1972	LOA provided. Referenced by FDA approved drug products. Adequate.
			Active since August 20, 2010	LOA provided. Referenced by FDA approved drug products. Adequate.
			Active since October 31, 2007	LOA provided. Referenced by FDA approved drug products. Adequate.
			Active since April 24, 2007	LOA provided. Referenced by FDA approved drug products. Adequate.
			Active since January 5, 2004	LOA provided. Referenced by FDA approved drug products. Adequate.

2.3 Drug Formulation

The drug product is a non-pressurized unit-dose nasal spray dispenser designed to deliver (b) (4) (or 0.1 mL) in a single spray. The drug product solution is filled into 125 mcL glass vials closed with rubber plungers. The vials are mounted into an (b) (4) unit-dose spray device that is commercially available. This unit-dose spray device does not require priming before use and the device can be used in any orientation. When the device is actuated the cannula of the actuator punctures the septum on the vial and delivers a (b) (4) (or 0.1 mL) spray of naloxone intranasal solution.

Figure 1: Naloxone Nasal Spray and How Administered



Composition of the naloxone hydrochloride 40 mg/mL nasal spray solution is presented in Table provided by the Sponsor below.

Table 1: Composition of NARCAN Nasal Spray

Concentration		40 mg/mL	
Component	Grade	Quantity per mL	Quantity per unit dose (100 µL)
Naloxone HCl dihydrate (corresponding to naloxone HCl)	USP	44.0 mg (40.0 mg)	4.4 mg (4.0mg)
Benzalkonium chloride (b) (4)	USP	(b) (4)	
Disodium edetate	USP		
Sodium chloride	USP		
Hydrochloric acid (b) (4)	USP		
Purified water	USP		

USP = United States Pharmacopeia
q.s. ad = a sufficient quantity to make

2.4 Comments on Novel Excipients

There are no novel excipients in the NARCAN nasal spray formulation. All of the excipients are listed in the FDA Inactive Ingredients Database (IID) and are present at lower levels¹ than contained in several FDA-approved nasal drug products.

Table 2: Excipients included in the drug product and qualification status

Ingredients	Function	Amount (mg/mL)	Maximum exposure of two sprays (ma/dav)	Acceptable? (Rationale)
Benzalkonium chloride	(b) (4)	(b) (4)	(b) (4)	YES (b) (4)
Disodium edetate				YES
Sodium Chloride				YES

IID: FDA Inactive Ingredients Database

2.5 Comments on Impurities/Degradants of Concern

Drug Substance Impurities

Adapt Pharma submitted specifications for naloxone hydrochloride substance (as shown below) that complies with the requirements of the United States Pharmacopeia (USP) and European Pharmacopoeia (EP) monographs:

¹ taking into consideration the concentration and daily intake associated with the designated maximum daily dose of 8 mg

Table 3: Applicant’s Drug Substance Specifications

Test	Acceptance criteria
Related substances (EP^{(b) (4)})	(b) (4)
Unknown related substances (each) Total related substances	(b) (4)
Assay (HPLC) ^{(b) (4)} Naloxone ^{(b) (4)}	(b) (4)

Reference is made to the ^{(b) (4)} DMF ^{(b) (4)} for details regarding the justification of the specifications of the drug substance. It is noted that the Sponsor has submitted two separate specifications that appear to conform to EP and USP guidelines but this Reviewer denotes the lowest specification below for review purposes and comments on the acceptability of the drug substance specification.

The identification threshold according to ICH Q3A(R2) for a maximum daily dose of a drug substance that is ≤ 2 g/day is 0.10% or 1.0 mg intake, whichever is lower. The qualification threshold according to ICH Q3A(R2) for a MDD of a drug substance that is ≤ 2 g/day is 0.15% or 1.0 mg total daily intake, whichever is lower.

The following Table illustrates the drug substance specifications (adapted from the Applicant’s submission) and adequacy of the specifications.

Table 4: Adequacy of Applicant’s Drug Substance Specifications

Impurity	Applicant’s Acceptance Criteria (%w/w)	ICH threshold	Acceptable?
[Redacted]	[Redacted]	ICH Q3A(R2) 0.15% or 1 mg, whichever is lower	Yes
			Yes
			Yes
			Yes
Unknown related substance	[Redacted]	ICH M7 NMT than 120 mcg/day	Yes; Contains an [Redacted] (b) (4) [Redacted] (b) (4) but the total daily intake is lower than 120 mcg/day as per ICH M7.
			Yes
N-oxide	Not detected; no specification	ICH Q3A(R2) 0.10%	Yes
[Redacted]	[Redacted]	Exceeds ICH Q3A(R2) 0.15% or 1 mg, whichever is lower	Yes; Although the specification is above the ICH qualification threshold, at this specification the daily intake would be [Redacted] (b) (4) (4). The DMF has been deemed acceptable for other FDA-approved naloxone drug products.
			Yes; Although the specification is above the ICH qualification threshold, at this specification the daily intake would be [Redacted] (b) (4) (4). The DMF has been deemed acceptable for other FDA-approved naloxone drug products.

Residual Solvents

The Applicant notes that naloxone hydrochloride final [Redacted] (b) (4) solvents present.
Several batches were screened for [Redacted] (b) (4)

levels were significantly below ICH solvent Option 1 guidelines and therefore has not proposed to test for these residual solvents. The acceptability of this justification is deferred to the CMC reviewer.

Drug Product

The Applicant has submitted the following drug product specifications for naloxone (see Table below provided by the Applicant).

Table 5: Applicant's Drug Product Specifications

Test Type	Method #	Test Using	Acceptance Criteria
Appearance of container	73.7320	Filled Vial	Clear glass vial with black plunger. No visual defects.
Appearance of container – device		Assembled Unit	Vial with plunger mounted in unit-dose device. No visual defect.
Appearance of formulation		Filled Vial	A clear and colorless or slightly yellow liquid.
Identity (UV)	73.7868	Filled Vial	The standard and sample spectra must be essentially identical from (b) (4)
Identity (HPLC)	73.7822	Filled Vial	Retention time of peak due to naloxone in the assay corresponds to that of the standard.
HPLC for Naloxone	73.7822	Filled Vial	(b) (4) % (of label claim)
HPLC for Benzalkonium chloride	73.7820	Filled Vial	(b) (4) %
HPLC for Disodium edetate	TS039	Filled Vial	%
pH	73.4011 (USP <791>)	Filled Vial	3.5 - 5.5
Osmolality	Current USP	Filled Vial	325-450 mOsm/kg
Uniformity of dosage units (as Uniformity of mass)	USP <905> current ed.	Assembled Unit	Per USP

It was noted in early development studies with naloxone solution that yellow discoloration occurred. Formation of this discoloration was confirmed to be independent of (b) (4) formation. However the Applicant eliminated this discoloration by the addition of EDTA and also noted that (b) (4) formation was absent.

As the maximum daily intake of intranasal naloxone is designated to be 8 mg, the identification threshold according to ICH Q3B(R2) for a maximum daily dose of a drug product that is 1 mg – 10 mg is 0.5% or 20 mcg intake, whichever is lower. The qualification threshold according to ICH Q3B(R2) for a MDD of a drug product administered per day between < 10 mg is 1% or 50 mcg total daily intake, whichever is lower.

Table 6: Adequacy of Applicant’s Drug Product Specifications

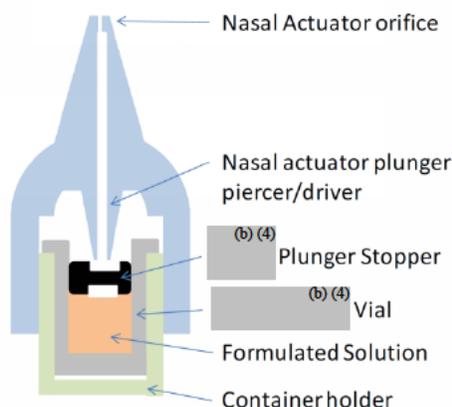
Degradant	Applicant’s Acceptance Criteria (%w/w)	ICH threshold	Acceptable?
	(b) (4)	ICH Q3B(R2) 1%	Yes
Unknown impurity	(b) (4)	ICH Q3B(R2) 0.5%	Yes
	(b) (4) Not detected; no specification		Yes

Container Closure System

NARCAN nasal spray consists of an (b) (4) unit dose actuator, with a glass vial and rubber stopper attached to the actuator. (b) (4) unit dose actuator is not part of the primary container closure system.

As seen in the Figure below, the vial/stopper provides a fully enclosed container-closure system. The Applicant submitted results from only an extractables study to support the safety of the container closure system.

Figure 2: Diagram of Naloxone Nasal Spray (not to scale)



Extractables Study (Report 2014001844 rev.1)

An extractables evaluation of (b) (4) plungers and glass vials was conducted to determine the extractable profile of the container closure system in direct contact with the drug solution. Extraction was performed on one lot of stoppers and one lot of vials in solvents of varying polarities that included, water, (b) (4). The stopper extracts were analyzed in duplicates by Liquid Chromatography/Mass Spectrometry (LC/MS), Gas Chromatography/Mass Spectrometry (GC/MS) direct injection and headspace, Ion Chromatography (IC) and Inductively Coupled Plasma/Optical Emission Spectroscopy (ICP/OES). Following were the extraction procedures utilized for this study (excerpt from Applicant’s submission):

Extraction Procedure for LC/MS (nonvolatile organic compounds) and GC/MS (semi-volatile organic compounds) Direct Injection
 About (b) (4)

prepared by refluxing the same volume of each solvent at the same conditions. After extraction, (b) (4) before being transferred to glass vials for storage until analysis.

GC/MS Headspace (volatile compounds)

About (b) (4) was put into GC headspace vials, in duplicate, and incubated at (b) (4) prior to injection. A blank was prepared by incubating an empty GC headspace vial at the same conditions.

Extraction Procedure for ICP/OES (extractable metals)

About (b) (4) were extracted, in duplicate, in (b) (4) was extracted at the same conditions. After extraction, the extracts were stored in (b) (4) tubes until analysis.

Extraction Procedure for IC (extractable anions)

About (b) (4) After extraction, the extracts were stored in (b) (4) tubes until analysis.

Extraction conducted with (b) (4) was considered by the Applicant to represent a “worst case scenario” and formed the basis of the risk assessment with respect to GC-MS and LC-MS results that were submitted to the NDA. It was noted in the submission by the Applicant that the extraction conditions with (b) (4) do not likely reflect real-life leaching due to the differences in the polarities, solvent strength, and temperature conditions. The Applicant reported the highest levels under any extraction conditions and created a summary table indicating the maximum theoretical exposure levels (see Table below).

Table 7: Extractables and Worst Case Estimates of Exposure

Compound	Exposure (mcg per 2 sprays) based on data from (b) (4) extracts	Genotoxic (Yes/No)	Risk
(b) (4)	(b) (4)	No	(b) (4)/WHO has indicated an acceptable ADI of 0.3 mg/kg bw (or 18 mg/day for 60 kg human)
		No	Common rubber (b) (4). Search in TOXNET did not reveal any information.
		No	Common rubber (b) (4). Search in TOXNET did not reveal any information.
		No	(b) (4)
		No	

(b) (4)		Selected as a leachable compound to be monitored over stability.
	Contains structural alert	Selected as a leachable compound to be monitored over stability.
	Contains structural alert	Selected as a leachable compound to be monitored over stability.
	No (b) (4)	13-week repeat-dose inhalational rat study noted clinical signs of salivation and rubbing and increased kidney and liver weights; NOAEL was considered to be 1300 ppm/6h/day (b) (4)
	No (b) (4)	(b) (4) mcg/day
	No (b) (4)	According to (b) (4), the total daily intake is 1.11 mg/kg bw/day (or 67 mg/day for 60 kg human), which derives mainly from roots and fish (b) (4)
	No (b) (4) however, classified as a possible human carcinogen (b) (4)	Selected as a leachable compound to be monitored over stability.
		Below FDA IID as an excipient
		Below FDA IID as an excipient
		Below FDA IID as an excipient (b) (4) estimates typical dietary intake of 20 to 50 mg/day (b) (4)
	No (b) (4)	F (b) (4) has set a PDI of 18-60 mg/day for a 60 kg human (b) (4)

*Potential leachables that will be monitored on long term stability samples

Table 8: Compounds Below the Toxicologic Threshold of Concern of 5 mcg/day

(b) (4)

Given that NARCAN nasal spray formulation is aqueous based, water extraction data appear to provide the most relevant representation of potential leachables. No peaks were detected in the water extracts analyzed by GC-MS or LC-MS. A potential confound is that the pH of the water was not specified in the extraction study report and that different results may be obtained in acid conditions, which is the case of NARCAN nasal spray that has a pH of 3.5 to 5.5. Other considerations are that extraction conditions are much harsher (i.e., temperature) than storage conditions and that the extraction study utilized whole stoppers in which the whole surface area of the rubber stopper is exposed to the solvent whereas in the case of the actual drug product only the base of the stopper under capped conditions is exposed to the aqueous drug solution.

To justify the safety of the container closure system, the Applicant notes that the (b) (4) plungers is utilized in a number of FDA-approved products and has also committed to conducting a leachables assessment that will monitor several compounds over stability, namely (b) (4)

(b) (4) Selection of these potential leachable compounds appears appropriate as the selection was based on the results from the extraction study. The Applicant states that three process validation batches will be placed on ICH stability and at selected time-points the samples will be analyzed for the proposed leachables. Any unknown peaks will be investigated to identify the analyte. Under real time (25°C/60%/RH) conditions leachables will be evaluated at 12 and 24 months and under accelerated conditions (40°C/75%/RH), leachables will be evaluated at 6 months.

Although a leachables assessment for this container closure system was requested, the absence of this data does not preclude approval for the following reasons: 1) the (b) (4) plungers is used in other FDA-approved aqueous based nasal and injectable drug products; 2) analysis of water extracts did not identify any substances; 3) the Applicant has committed to monitor for leachables during stability; 4) this product is indicated for acute, single-use, and 5) the product for a potentially life-saving therapy.

2.6 Proposed Clinical Population and Dosing Regimen

NARCAN intranasal naloxone is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Adapt Pharma in collaboration with National Institutes for Drug Abuse

(NIDA) developed this user friendly intranasal product to expand use and distribution of naloxone, in particular to laypersons outside medical settings. NARCAN nasal spray is intended for immediate use as emergency therapy in settings where opioids may be present for use in both adult and pediatric patients. The following excerpt is from the proposed labeling:



Each nasal spray device will deliver 4 mg of naloxone hydrochloride solution in a delivery volume of (b) (4) (or 0.1 mL). The proposed dose is one spray but as stated in the label additional doses of NARCAN nasal spray may be administered to alternating nostrils. A dose of 8 mg/day (two sprayers) will be used as the reference human daily dose.

2.7 Regulatory Background

The Applicant has filed a 505(b)(2) application for NARCAN nasal spray that relies upon the findings of safety and efficacy of intranasal naloxone from published scientific literature. This NDA application was accepted for rolling review and was granted priority review.

Adapt Pharma has obtained the rights to the original NARCAN NDA (N16636) with the associated naloxone product withdrawn from the market but not for reasons of safety or

efficacy. Naloxone hydrochloride was originally approved as NARCAN in 1971 for the treatment of known or suspected narcotic overdose via the IV, IM, or SC route of administration but has never received FDA approval for intranasal use. According to the original NARCAN product label, the usual initial dose is 0.4 mg to 2 mg that may be administered IV. This dose may be repeated at 2 to 3 minute intervals if the desired degree of opioid antagonism is not obtained. If no response is noted after a dose of 10 mg has been administered, the diagnosis of “narcotic” overdose should be reconsidered.

The Division discussed the nonclinical development program of intranasal naloxone on two occasions at a PIND and a preNDA meeting that took place on May 24, 2012 and March 27, 2015, respectively. Briefly at these meetings, the Division stated that although naloxone is not approved for the intranasal route of administration, no new nonclinical studies would be required to support clinical studies or for an NDA because of prior clinical experience with intranasal naloxone, proposed dose of NARCAN intranasal spray is within the approved dose of NARCAN, a lack of novel excipients² in the drug product formulation, and commitment that local safety of the intranasal naloxone would be evaluated based on clinical monitoring of local tissues. It was also communicated to the Applicant that adequate justification for the safety of the drug substance specifications, the drug product degradants, the excipients used in the drug product formulation and the container closure system in terms of leachables and extractables were required for the NDA submission. At the preNDA meeting, the Applicant notified the Division that an extractables study along with a risk assessment would be submitted to the NDA. The Division recommended that leachables be monitored on stability and recommended that any known data concerning the stopper extractables be submitted to the NDA.

In general, the Applicant has addressed all of the Division’s recommendations in the submitted NDA and has committed to monitoring several identified leachables during stability, which is deemed acceptable (see conclusion of Section 2.5 for additional information and rationale for the acceptability of this approach).

In June 2015, the Agency agreed to the pediatric study plan with no requirements for any nonclinical juvenile studies.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical toxicology studies were submitted with this NDA or required for this 505(b)(2) application. As requested, the Applicant conducted and submitted a literature

² *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration.*

review of published data to determine if there were new data that may impact the safe use of this drug product. The submitted literature publications were reviewed to determine if the data were adequate and whether the new information or data impacted product labeling.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

There were no previous reviews of this NDA.

4 Pharmacology

4.1 Primary Pharmacology

There were no new pharmacology/toxicology studies with naloxone submitted or required for this 505(b)(2) application. The original NARCAN label states:

NARCAN prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension. Also, NARCAN can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

NARCAN is an essentially pure opioid antagonist, i.e., it does not possess the “agonistic” or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

NARCAN has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, NARCAN will produce withdrawal symptoms. However, in the presence of opioid dependence, opiate withdrawal symptoms may appear within minutes of NARCAN administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of NARCAN and to the degree and type of opioid dependence. While the mechanism of action of NARCAN is not fully understood, in vitro evidence suggests that NARCAN antagonizes opioid effects by competing for the μ , κ , and σ opiate receptor sites in the CNS, with the greatest affinity for the μ receptors.

High doses of naloxone can block the effects of endogenous opioid tone in the body. As endogenous opioid tone is generally low in healthy individuals, most of these effects are not believed to have clinical significance. However, naloxone may result in mild dysphoria. As endogenous opioids also regulate pituitary secretion, naloxone can result in increased gonadotropin-releasing hormone and corticotrophin-releasing factor resulting in elevations of plasma luteinizing hormone, follicle stimulating hormone and ACTH. Opioid antagonists may increase prolactin secretion in women and augment stress or exercise-induced cortisol and catecholamine release (Gutstein and Akil, 2001).

As per the warnings and precautions section of naloxone labeling, underlying cardiovascular disease may be at greater risk due to the potential for catecholamine release in opioid tolerant individuals. In addition, naloxone may augment seizures in patients with a history of seizures.

4.2 Secondary Pharmacology

There were no new pharmacology/toxicology studies with naloxone submitted or required for this 505(b)(2) application.

Naloxone has been reported to influence pharmacological responses to a variety of non-opioid drugs by antagonizing the secondary effects with some effects unrelated to the direct occupation of opioid receptors. For example naloxone at high doses appears to act as an antagonist at the gamma aminobutyric acid (GABA) receptor and has been implicated in the convulsant properties associated with high doses in mice (Dingledine et al., 1978; Svensson et al., 2000). A dose of approximately 150 mg/kg of naloxone administered to mice intraperitoneally produced convulsions in approximately 10% of animals injected (Dingledine et al., 1978), which corresponds to HED of 731 mg for a 60 kg person.

4.3 Safety Pharmacology

There were no new pharmacology/toxicology studies with naloxone submitted or required for this 505(b)(2) application.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There were no new nonclinical studies with naloxone submitted or required for this 505(b)(2) application.

5.2 Toxicokinetics

There were no new nonclinical studies with naloxone submitted or required for this 505(b)(2) application.

6 General Toxicology

There were no new toxicology studies with naloxone submitted or required for this 505(b)(2) application.

The proposed dosing is within the FDA-approved dose range for opioid overdose. There are no systemic general toxicology concerns with the proposed dosing protocol.

7 Genetic Toxicology

There were no new genetic toxicology studies with naloxone submitted in this NDA or required for this 505(b)(2) application.

According to the FDA approved Narcan drug product labeling (Endo, July 2003):

NARCAN 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.

8 Carcinogenicity

There were no carcinogenicity studies with naloxone submitted in this NDA or required as the proposed drug product is for acute use.

According to the FDA approved Narcan drug product labeling (Endo, July 2003):

Studies in animals to assess the carcinogenic potential of NARCAN have not been conducted.

9 Reproductive and Developmental Toxicology

There were no new reproductive and developmental toxicology studies with naloxone submitted or required for this 505(b)(2) application.

Information and data regarding the effects of naloxone on reproduction and development can be divided into three sources, which include the original NARCAN label, developmental and reproductive toxicology studies³ contained in NDA 16636, and published literature.

Original NARCAN label

According to the FDA approved Narcan drug product labeling (Endo, July 2003):

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/m²), demonstrated no embryotoxic or teratogenic effects due to NARCAN.

Use in Pregnancy

Teratogenic Effects: Pregnancy Category C

³ Adapt Pharma owns the rights to NDA 16636

Teratology 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/m²), demonstrated no embryotoxic or teratogenic effects due to NARCAN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

Non-teratogenic Effects

Risk-benefit must be considered before NARCAN is administered to a pregnant woman who is known or suspected to be opioid-dependent since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta, and may precipitate withdrawal in the fetus as well as in the mother. Patients with mild to moderate hypertension who receive naloxone during labor should be carefully monitored as severe hypertension may occur.

Studies conducted under NDA 16636

Data from fertility and embryonic development, embryo-fetal development, and pre- and post-natal developmental reproduction studies in rats and an embryo-fetal study in mice were previously submitted to support NDA 16636, which was previously reviewed (see nonclinical review by Dr. Edward Tocus dated May 12, 1969) and are adapted below from his review. The original studies were not re-reviewed and the conclusions from the original reviewer, who examined the original study reports, are not being reconsidered.

9.1 Fertility and Early Embryonic Development

Methods

Doses:	0 (saline), 2, 10 mg/kg
Frequency of dosing:	Daily
Dose volume:	Not specified in nonclinical review.
Route of administration:	Subcutaneous injection
Vehicle:	Appears to be saline
Species/Strain:	Rats/CFE
Number/Sex/Group:	Not specified in nonclinical review.
Satellite groups:	Not specified in nonclinical review.
Study design:	Males were administered 60 days before mating beginning at 50 days old while females were administered 14 days prior to mating when 96 days old. One male was mated with two females receiving the same dose. The females were continued on drug throughout the study. One-half the females were killed on Day 13 of gestation with the remaining females were allowed to litter normally.
Deviation from study protocol:	It appears from the nonclinical review that rats were moved during the study due to a labor dispute as reported by the Sponsor. This was a

significant deviation as survival was drastically reduced in all groups.

Observations and Results

Former PT reviewer concluded that "there were no differences in control and treated rats in their ability to reproduce."

	Dose (mg/kg)		
	Saline	2	10
Percent pregnant	77	73	78
Mean Implantations day-13	12.7	9.2	10.0
Mean Resorptions day-13	0.7	0.5	0.1
Fetuses/dam day-13	12.0	8.7	9.9
Pups/litter natural birth	8.5	7.8	7.7
% Stillborn	29	17	26
Pups born alive	89	78	62
Alive at 21-days	66	36	29
Avg. birth weight (gms)	6.0	6.2	5.7
Malformations	0	0	0

Reviewer Comment: Moving the animals during the course of study clearly complicates interpretation of the study results. The move would likely be a stressful event on the dams and the fetuses and the presence of the naloxone could have had an adverse impact on their adaptability to that stress. The apparent reduced pup survival at 21-days is difficult to interpret given the unknown denominator. There did not appear to be any treatment related increase in post-partum pup losses at PND 21 in the Segment 3 study reported below. The original review concluded that there were no adverse effect and the findings were not included in the original labeling.

9.2 Embryonic Fetal Development

Mice

Methods

Doses: 0 (saline), 2, 10 mg/kg/day
 Frequency of dosing: Daily
 Dose volume: Not specified in nonclinical review.
 Route of administration: Subcutaneous
 Vehicle: Appears to be saline
 Species/Strain: Mice/CF-1
 Number/Sex/Group: 20 pregnant mice/group
 Satellite groups: Not specified in nonclinical review
 Study design: Dosing was from Gestational Day 6 to Day 15. Females were sacrificed on Day 18 and fetuses obtained by Cesarean section. One-third of the fetuses were fixed for visceral examination with

the remaining cleared and stained for skeletal examination.

Deviation from study protocol: Not specified in nonclinical review.

Observations and Results

Former PT reviewer concluded that “no pharmacological effects were observed in the mothers. No difference between control and treated was observed in numbers of resorption sites, live fetuses or in fetal weights. Visceral and skeletal abnormalities usually seen in mice were observed in control and treated groups not related to drug.”

Rats

Methods

Doses: 0 (saline), 2, 10 mg/kg/day
 Frequency of dosing: Daily
 Dose volume: Not specified in nonclinical review.
 Route of administration: Subcutaneous
 Vehicle: Appears to be saline
 Species/Strain: Rats/CD
 Number/Sex/Group: 20 pregnant mice/group
 Satellite groups: Not specified in nonclinical review
 Study design: Dosing was from Gestational Day 5 to Day 14. Females were sacrificed on Day 19 and fetuses obtained by Cesarean section. One-third of the fetuses were fixed for visceral examination with the remaining cleared and stained for skeletal examination.

Deviation from study protocol: Not specified in nonclinical review.

Observations and Results

Former PT reviewer concluded that “no pharmacological or toxicological effects were seen in the dams. Implantation, resorption, litter size, fetal weight and length were the same in treated and control. No visceral abnormalities were observed. No unusual skeletal abnormalities were observed although the high dose (10 mg/kg) caused some delay in ossification.”

9.3 Prenatal and Postnatal Development

Methods

Doses: 0 (saline), 2, 10 mg/kg/day
 Frequency of dosing: Daily
 Dose volume: Not specified in nonclinical review.
 Route of administration: Subcutaneous injection
 Formulation/Vehicle: Appears to be saline
 Species/Strain: Rats/CFE

Number/Sex/Group: 20 pregnant rats/group
 Satellite groups: Not specified in nonclinical review
 Study design: Dosing was administered from Gestational Day 15 until weaning at Postnatal Day 21. Specific endpoints and necropsy dates were not specified in the nonclinical review.

Deviation from study protocol: Not specified in nonclinical review.

Observations and Results

Former PT reviewer concluded that "No effect of the drug was observed on the dams, all deliveries were normal."

	Dose (mg/Kg)		
	Saline	2	10
Total pups/litter	195/20	189/20	205/20
Avg. pups/litter	9.8	9.4	10.3
No. pups stillborn	3	16	6
No. pups alive at day-21	169	125	177
Avg. birth weight (g)	6.3	6.3	6.8
Avg. g _m weight at day-21	38.9	38.1	39.7

Published Literature

The Sponsor identified five published articles (Hetta and Terenius, 1980; Jurand, 1985; Shepanek et al., 1989; Rocha-de-Melo et al., 2008; Sobor et al., 2011) that evaluated the effects of naloxone on reproductive and developmental endpoints. A review conducted by the Division also identified several additional publications (Vorhees et al., 1981; Suzuki et al., 1988; Dobryakova et al., 2005; Weber et al., 2006). Collectively these publications are summarized and discussed below.

Published Title: Prenatal naloxone affects survival and morphine sensitivity of rat offspring (Hetta and Terenius, 1980)

Methods: Sprague Dawley (SD) rats were fitted with a subcutaneous minipump during Gestation Day 11 or Day 17 or Postpartum Day 3. Saline or naloxone at 30 or 100 mg/mL was released from the pump at a constant rate of 0.033 or 0.1 mg/h for a period of 7 days. Onset of parturition was noted and the number of pups live or stillborn counted. At 36 h post-delivery, litters were weighed and stillborn or dead pups removed. If number of pups exceeded nine, the litters were culled to nine, equalizing the number of females and males if possible. The pups were weighed weekly with pups weaned on PND 21.

Results: Implantation of pumps to the mothers Postpartum Day 3 did not affect pups with no effects on body growth. Neonatal mortality was significantly increased in the group that received naloxone 0.1 mg/h from Gestational Day 17 compared to saline

controls (see Table below). Body weights were slightly decreased by administration of naloxone 0.03 mg/h starting on Gestation Day 17.

Group A: G17; Group B: G17; Group C: G11; Group D: G17; Group E: G17; Group F: G11

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Pups born from dams treated with naloxone did not differ in response to the hotplate test. However pups demonstrated a greater sensitivity to low dose morphine-induced antinociception. The clinical significance of these results is difficult to extrapolate as the dosing was via continuous infusion subcutaneously versus single-administration in the case of NARCAN nasal spray. The authors of this paper stated that the higher dose level of 0.1 mg/h received 2.4 mg/day or approximately 7 mg/kg/day, which corresponds to a HED of 68 mg/day for a 60 kg human based on body surface area.

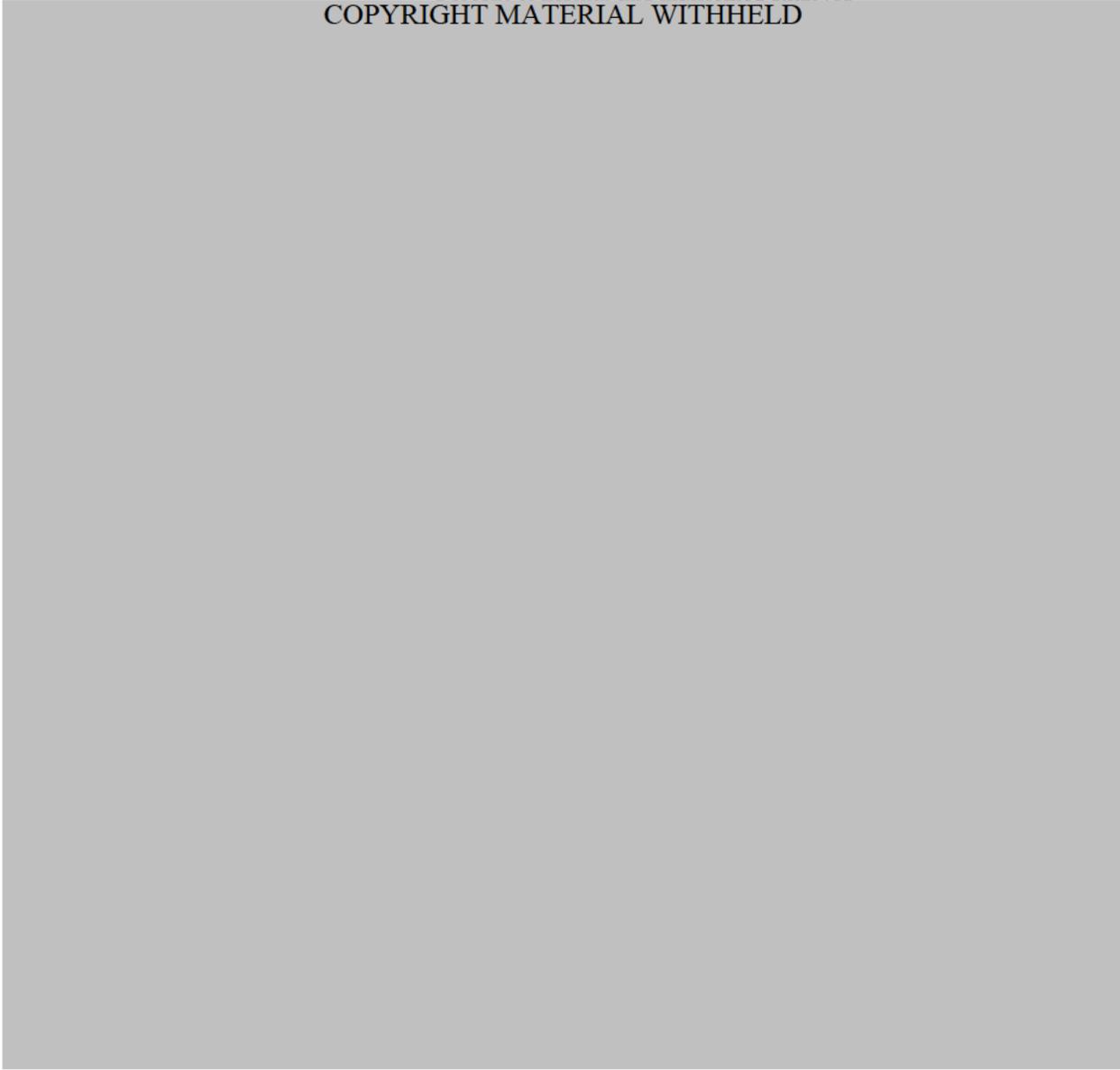
Publication Title: The interference of naloxone hydrochloride in the teratogenic activity of opiates (Jurand, 1985)

Methods: Naloxone was administered to 8-10 pregnant female JBT/Jd mice on Gestational Day 9 at doses of 25, 40, 80, 120, or 200 mg/kg, IP. In other groups, diamorphine (65 mg/kg), methadone (19 mg/kg), and the synthetic enkephalin analogue FK 33-824 (60 mg/kg) were administered to pretreated pregnant females with either saline or naloxone to determine whether pretreatment with equimolar doses of the antagonist naloxone (see table below) applied 30 min prior to treatment with the opioid agonists antagonizes opioid agonist induced malformations. All pregnant mice were sacrificed on Gestational Day 13 with fetuses dissected and fixed in utero and all malformations were recorded.

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Results: Administration of naloxone at doses up to 200 mg/kg was not embryotoxic nor did naloxone produce any teratogenic activity. Pretreatment with equimolar doses of naloxone administered 30 min prior to administration of opioid agonists, resulted in a significant reduction in the occurrence of malformations of the central nervous system, which included kinking of the spinal cord, exencephaly, craniorachischisis, and brachyury (see table below). In contrast, dilatation of the fourth brain ventricle was not affected by pretreatment of naloxone.

Percent of normal and malformed embryos
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The NOEL identified in this study was 200 mg/kg naloxone, which corresponds to a HED of 16 mg/kg based on body surface area or 975 mg for a 60 kg human.

Publication Title: Behavioral and neuroanatomical sequelae of prenatal naloxone administration in the rat (Shepanek et al., 1989)

Methods: Pregnant Long-Evans Hooded rats received daily subcutaneous injections of either 1 or 5 mg/kg naloxone or vehicle (saline) from Gestational Day 4 to Gestational Day 18. At delivery, litters were culled to 4 males and 4 females. Offspring were assessed for development of righting reflex, negative geotaxis, open field activity, and acquisition of a Warden maze. Offspring sacrificed at Postnatal Day 21 were assessed for several parameters of cerebellar, hippocampal, and motor cortical morphology.

Results: Administration of naloxone to pregnant rats from GD 4 to GD 18 did not produce any effects on maternal weights, pup survival, pup weight, or sex distribution.

**PREGNANCY AND BIRTH MEASURES (MEANS \pm SEM)
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Naloxone at 5 mg/kg/day accelerated development of negative geotaxis and right reflex whereas a dose of 1 mg/kg/day resulted in impairments. In a Warden maze, low dose naloxone resulted in females having significantly more errors than controls on the first day of maze learning. No morphological effects in the motor cortex, cerebellum, and hippocampus were observed with the exception of 5 mg/kg/day naloxone, which produced higher concentration of granule cells in the curvature of the dentate gyrus as compared to controls. The results from this study indicate that prenatal exposure to naloxone may later neurobehavioral development in the rat. Doses of 1 and 5 mg/kg/day correspond to HED of 0.16 mg/kg (9.7 mg per 60 kg human) and 0.8 mg/kg (48 mg per 60 kg human), respectively.

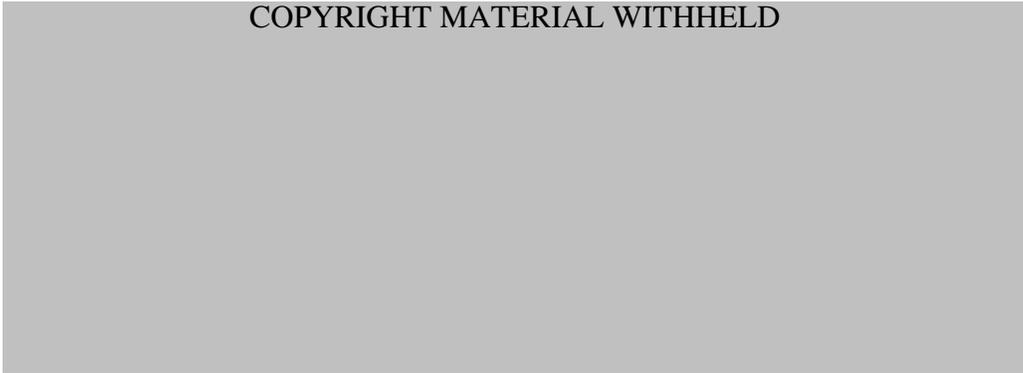
Publication Title: Chronic neonatal exposure of rats to the opioid antagonist naloxone impairs propagation of cortical spreading depression in adulthood (Rocha-de-Melo et al., 2008)

Methods: Wistar male rats from Postnatal Day 7 to Postnatal Day 28 were treated daily with a single subcutaneous injection of 10 mg/kg/day naloxone or saline (10 mL/kg). Cortical spreading depression (CSD) was recorded in young pups aged PND 30 to PND 40 and adult rats aged PND 90 to PND 120 that were anesthetized with a mixture of 1 g/kg urethane plus 40 mg/kg chloralose intraperitoneally. A tracheal

cannula was inserted and three trephine holes were made on the right side of the skull. One hole was used to apply the stimulus by a 1 min application of a cotton ball soaked with 2% KCl and two other holes were used to record the propagating CSD wave.

Results: CSD propagation velocity was decreased in both young and adult groups that were treated with naloxone as compared to animals treated with saline.

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A NOAEL was identified as only one dose of 10 mg/kg/day was evaluated. This dose of naloxone corresponds to HED of 1.6 mg/kg or 97 mg naloxone in a 60 kg human based on body surface area comparison.

Publication Title: Effects of opioid agonist and antagonist in dams exposed to morphine during the perinatal period (Sobor et al., 2011)

Methods: Pregnant Wistar rats were administered morphine or saline once daily subcutaneously during gestation and lactation, a period at least 21-22 days. Morphine was administered at a dose of 5 mg/kg/day on the first two days and then 10 mg/kg/day afterwards. Physical and behavioral signs of morphine withdrawal were investigated both in the early postpartum period (maternal behavior) and after weaning (physical signs, locomotion, anxiety-like behaviors). Maternal behavior was evaluated after acute challenge with naloxone (3 mg/kg, SC) or morphine (10 mg/kg, SC) and morphine (10 mg/kg, SC) plus naloxone (3 mg/kg, SC).

Results: Maternal behavior was not affected by naloxone (3 mg/kg) alone but impaired maternal behavior in morphine-treated dams. Naloxone precipitated moderate physical withdrawal signals in morphine-treated dams, while anxiety and locomotor activity after administration of naloxone were not changed.

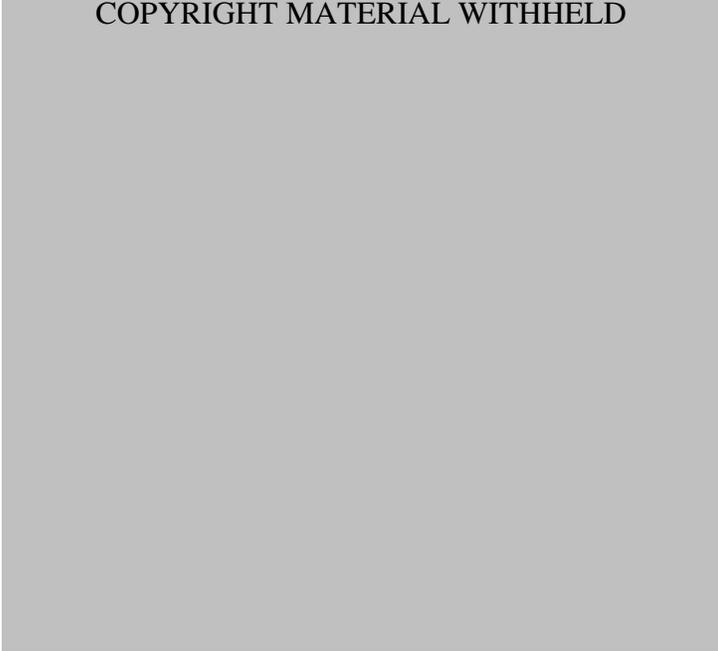
Publication Title: Effects of prenatal naloxone exposure on postnatal behavioral development of rats (Vorhees, 1980)

Methods: Pregnant Sprague-Dawley rats were administered either 40 mg/kg/day of naloxone or saline intraperitoneally in two divided doses (7 h between dosing) on Gestational Day 7 to Gestational Day 20. Dams were weighed weekly during gestation and daily during treatment and at parturition each litter was examined for the presence

of dead or malformed pups. Dams and offspring were weighed weekly through weaning (PND 21) and offspring biweekly thereafter. Behavioral testing began on PND 3 and extended into adulthood PND 120. Birth litters with less than 8 progeny were eliminated from the experiment and those with more than 8 were reduced to 4 males and 4 females. Offspring were examined for physical milestones (testicular appearance, incisor eruption, eye opening, vaginal patency) and neurobehavioral measures (surface righting, swimming development, negative geotaxis, pivoting assessment, olfactory orientation, auditory startle, open field, spontaneous alternation, passive avoidance, food grasping, tail flick, activity wheels, rotorod, active avoidance, M-maze and Biel maze).

Results: Prenatal naloxone administration (GD7 to GD 20) had no significant effects on maternal weight, number of small litters, gestation length, litter size, sex distribution, and offspring mortality. However, administration of naloxone resulted in accelerated postweaning growth, upper incisor eruption, righting development, startle development, home scent discrimination, and in directional swimming and as adults, impairments in Biel water maze learning. No differences were reported in other postweaning tests including open field, running wheel, M-maze, spontaneous alternation, active or passive avoidance, rotorod, food grasping or tail flick.

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A NOAEL for the impairment in Biel water maze and accelerated development was not identified. The tested dose of 40 mg/kg/day corresponds to a HED of 6.45 mg/kg or 387 mg in a 60 kg human, based on body surface area.

Publication Title: Changes of monoamine and TRH contents in naloxone induced inhibited development of rat cerebrum and cerebellum (Suzuki et al., 1988)

Methods: Newborn Sprague-Dawley rats were administered subcutaneous injections of either 1 or 50 mg/kg naloxone or saline daily until weaning (PND 21). After a week from the last injection, animals were sacrificed and brains and spinal cords rapidly removed and dissected. Levels of monoamines and their metabolites and thyrotropin-releasing hormone (TRH) were measured in different parts of the brain.

Results: Postnatal administration of naloxone from birth to weaning (PND 1 to PND 21) resulted in a dose-dependent decrease in cerebral and cerebellar weights with a reduction in body weights only observed in the high dose group. However, morphological changes or changes in movement were not observed in naloxone treated animals. Serotonin was decreased in the cerebral cortex and medulla and increased in the post and striatum of naloxone treated animals. Noradrenaline was decreased in the medulla but increased in the pons of naloxone treated animals. TRH was decreased in the cerebellum and hippocampus of naloxone treated animals. The authors suggest that neurotransmitters influence brain development that is modulated by endogenous opioid system. Naloxone doses of 1 and 50 mg/kg/day corresponds to HED doses of 0.16 mg/kg or 9.7 mg for a 60 kg human and 8.1 mg/kg or 484 mg for a 60 kg human based on body surface area, respectively.

Publication Title: Effect of opioid antagonist naloxone on maternal motivation in albino rats (Dobryakova et al., 2005)

Methods: Maternal behavior was observed on Postnatal Day 4 to Day 6. Ten min prior to testing, females were injected with distilled water (PND 4 and 6) or administered aqueous solution of naloxone (PND 5) either via an intraperitoneal injection at doses of 1 or 5 mg/kg (1 mL/kg) or instillation into the nasal cavity at doses of 0.2, 1.0 and 5.0 mg/kg (100 mcL/animal). Maternal reactions were evaluated in two three sessions. Session 1 included the open field test with spontaneous exploratory activity (running, rearing, grooming etc.) recorded in red light. During Session 2 three rat pups were placed at the center of the arena and latency of the first approach, total number of approaches, number of transfers of pups, and latency of the third pup were recorded under red light. During the last session, the same parameters were evaluated at bright illumination.

Results: A single intraperitoneal injection of naloxone at a dose of 5 mg/kg on PND 5 increased the number of approaches to pups, decreased the latency of their transfer into a new location, which are measures of maternal behavior. Similarly intranasal naloxone at a dose of 1 mg/kg produced similar changes. It was noted that naloxone injected IP modified the number of approaches to the pups while after intranasal administration the number of pup transfers were altered in a more marked manner. The changes in maternal behaviors are not considered adverse by this Reviewer.

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Effect of naloxone (IP versus IN) on maternal behaviors at red dim (light bars) and bright illumination (dark bars). 1) 1 mg/kg intraperitoneally; 2) 5 mg/kg naloxone intraperitoneally; 3) 0.2 mg/kg naloxone intranasally; 4) 1 mg/kg naloxone intranasally; 5) 5 mg/kg naloxone intranasally.

The authors indicate that naloxone administration may enhance maternal motivation in post-partum psychosis and depression. The NOEL was identified to be 1 mg/kg intraperitoneally and 0.2 mg/kg intranasally, which correspond to HED of 9.7 mg IP and 1.9 mg IN, respectively.

Publication Title: Opioid receptors regulate retrieval of infant fear memories: Effects of naloxone on infantile amnesia (Weber et al., 2006)

Methods: Naloxone, naloxone methiodide or saline were subcutaneously administered to Sprague-Dawley rats (PND 17-18) at various timepoints during contextual fear conditioning. Rats were placed into an experimental chamber for 120 seconds and then received a 1 second, 0.6 mA footshock. Rats were removed after 30 seconds and returned to their home cage either directly or after receiving a drug injection.

Results: Subcutaneous injection of naloxone at a dose of 5 mg/kg prior to testing and 7 days prior to testing, but not immediately after training, blocked infantile amnesia. Normally when rats are subjected to a shock in the fear conditioning apparatus, animals freeze when animals are returned to the same context 1 minute after training because they remember and expect a shock. When animals are returned to the apparatus 24 hours later, freezing is reduced indicating that animals do not remember the context in which it was shocked, which describes an active process of infantile amnesia. Because naloxone caused increased freezing as compared to saline when administered prior to testing, the authors believe that endogenous opioids regulate the retrieval of infant fear memories which contributes to an active process known as infantile amnesia. A NOAEL was not identified in this study as the only dose of 5 mg/kg evaluated blocked infantile amnesia. This dose corresponds to an HED of 48 mg for a 60 kg human.

Summary

Collectively these published studies have evaluated the effects of naloxone on reproduction and developmental endpoints and suggest that naloxone can potentially impact the central nervous system. However in most cases, the doses were significantly higher than NARCAN intranasal spray. It is important to note that there was no significant adverse effect identified in these published studies that would negate the benefit of this potentially life-saving therapeutic, given that an opioid agonist itself also have been demonstrated to have adverse impact on brain development. In agreement with the Sponsor, this Reviewer feels that the results of the articles and literature search do not impact the safety or labelling of NARCAN nasal spray.

10 Special Toxicology Studies

There were no new special toxicology studies with naloxone submitted in this NDA or required for this 505(b)(2) application.

Currently there are no intranasal naloxone products approved by FDA. Local tolerance studies in two species of adequate duration would normally be required to support clinical studies and an NDA. However, the Division indicated that no new studies for naloxone would be required so long as the intranasal local tissue reaction was characterized in the clinical setting. Adapt has submitted an assessment of local tolerance based on clinical monitoring of local tissues and the reader is referred to the Medical Officer review for the assessment of local safety of NARCAN intranasal spray. It is noted by the Applicant that a literature search for toxicology studies conducted with nasal naloxone revealed no studies.

11 Integrated Summary and Safety Evaluation

The Applicant has submitted a 505(b)(2) NDA for NARCAN intranasal spray for the emergency treatment of opioid overdose. No new toxicology studies for naloxone were required to support this application. Although intranasal toxicology studies would normally be required to support a reformulated drug product that employs an alternate route, the Division determined that nonclinical studies would not be required given the large clinical experience with intranasal use of naloxone, the acute use of the drug product, and the potentially life-saving indication.

Safety of the drug substance and drug product specification was adequately addressed in the application. With regards to the safety of the container closure system, the Applicant submitted results from an extractables study that indicated no extractable substances were detected under refluxing conditions with water utilized as the solvent. The previous use of this container closure system in other FDA-approved intranasal and injectable products as well as the lack of compounds from water extracts under harsh conditions suggest there are no safety concerns for the container closure system used in this acute-use potentially life-saving therapy. Moreover, the Applicant has stated that potential leachables will be assessed in long-term stability batches. Therefore the lack of leachable data from long-term stability data is not considered an approval issue but

additional leachables testing at several timepoints over stability evaluating multiple batches as a post-marketing commitment is warranted. Following review of the published nonclinical literature, there were no significant new information regarding the safety, effectiveness of naloxone that impacted the labeling of NARCAN nasal spray.

12 Appendix/Attachments

Reference List

Dingledine R, Iversen LL, and Breuker E (1978) Naloxone as a GABA antagonist: evidence from iontophoretic, receptor binding and convulsant studies. *Eur J Pharmacol* **47**:19-27.

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[REDACTED] (b) (4)

[REDACTED] (b) (4)

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[REDACTED] (b) (4)

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Zeiger E, Anderson B, Haworth S, Lawlor T, and Mortelmans K (1992) Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ Mol Mutagen* **19(Suppl 21)**:2-141.

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/s/

NEWTON H WOO
11/02/2015

RICHARD D MELLON
11/02/2015

I concur with Dr. Woo's recommendation that NDA 208411 may be approved from a nonclinical pharmacology toxicology perspective. I also concur with the proposed labeling changes and the recommendation for the PMC.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 208411

Applicant: Adapt Pharma Inc.

Stamp Date: July 20, 2015

**Drug Name: Nasal Naloxone
Spray**

**NDA/BLA Type: 505(b)(2)
referencing literature. They list
Narcan as the referenced product,
but they now own it.**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		No new nonclinical toxicology studies were required for this b2 application. Labeling will have to be updated as there are potential b2 implications regarding referenced drug products. After a TCON with the Applicant (8/21/2015), the annotated label was updated in an amendment to the NDA (dated 8/25/2015) that resolved the previously identified labelling issue.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		X	Not applicable. See above.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?		X	Not applicable. See above.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		X	Not applicable. See above.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		NDA contains safety justification for drug substance, drug product specifications and for the safety of the container closure system.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	-	-	Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		Although submitted as a 505(b)(2) application referencing Narcan and literature, they now own Narcan. Therefore, this is a 505(b)(2) to literature. The literature review was included to update knowledge since the 1971 approval of Narcan. The need for these published data to support approval; however, will be a review issue.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no review issues that need to be forwarded to the Applicant at this time.

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

/s/

NEWTON H WOO
08/26/2015

RICHARD D MELLON
08/26/2015