CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208411Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval
NDA: 208411

NDA 208411
Review #1

Drug Name/Dosage Form	Naloxone Nasal Spray
Strength	40mg/ml
Route of Administration	Nasal Spray
Rx/OTC Dispensed	Rx
Applicant	Adapt
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Venkat Pavuluri	OPQ/ONDP/DNDPAPI/BII
Drug Product	Venkat Pavuluri	OPQ/ONDP/DNDPII/BIV
Process	Christina Capacci-Daniel Edwin Rao	OPQ/OPF/DIA/IAB2
Microbiology	Christina Capacci-Daniel Erika Pfeiler	OPQ/OPF/DIA/IAB2
Facility	Christina Capacci-Daniel Grace McNally	OPQ/OPF/DIA/IAB2
Biopharmaceutics	NA	
Regulatory Business Process Manager	Steve Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Julia Pinto	OPQ/ONDP/DNDPII/BIV
CDRH OC Combination Products	Juandria Williams	
Environmental Assessment (EA)		

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	Naloxone	Adequate	Oct 2015	
	Type III *(if applicable)*		Nasal spray device	Adequate	October 2105	
	Type IV *(if applicable)*					
	Other					

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH		Adequate with PMCs	Oct 2015	Ryan McGowen Rick Chapman
Clinical				
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Narcan®(Naloxone Hydrochloride) Nasal Spray is intended for use in the emergency treatment of opioid overdose and therefore was granted fast track designation. The naloxone API is supplied by (b) (4). The drug product is formulated (b) (4) comprising the following excipients: Sodium chloride, disodium edetate, and benzalkonium chloride, in a concentration of 40mg/ml. The container closure system is a glass vial with a (b) (4) stopper which is then encased within a nasal actuator and container holder. The nasal spray device is by (b) (4) under DMF (b) (4) and has been reviewed by CDRH and OPQ, for use with the naloxone drug product. Each unit dose device, formulated to deliver one dose of naloxone, is placed within a blister package. Two units or blister packages are then stored per carton. Adequate data to assess the device delivery of the drug product and to assure the identity, strength, purity, and quality of the drug product is provided. The drug product is granted an expiry of 24 months, when stored at room temperature. Further, the Office of Process and Facilities, has made an overall recommendation of adequate for all facilities related to this application. Therefore, from a quality perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Conduct a Stability study for the Drug Product stored at 4°C and 40°C for 24 months, to support the storage and excursion statement on the carton and insert labels.

Two additional PMCs are have been agreed upon, by CDRH review team and the Sponsor. See CDRH Review by Ryan McGowen.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Julia C. Pinto -S

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Start of Sponsor material

NARCAN (naloxone hydrochloride) NASAL SPRAY
Adapt Pharma Operations Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NARCAN nasal spray safely and effectively. See full prescribing information for: NARCAN nasal spray.

NARCAN (naloxone hydrochloride) nasal spray (b) (4)
Initial U.S. Approval: (b) (4)
(b) (4)

INDICATIONS AND USAGE
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. (1)
NARCAN nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present. (1)
(b) (4)
NARCAN nasal spray is not a substitute for emergency medical care. (1)

DOSAGE AND ADMINISTRATION
- NARCAN nasal spray is for intranasal use only. (2.1)
- Seek emergency medical care immediately after use. (2.1)
- Administer a single spray of NARCAN nasal spray to adults or pediatric patients (b) (4) into one nostril. (2.2)
- (b) (4)

DOSAGE FORMS AND STRENGTHS
(b) (4)

CONTRAINDICATIONS
(b) (4) hypersensitive to naloxone hydrochloride (4)

WARNINGS AND PRECAUTIONS
(b) (4)

ADVERSE REACTIONS
(b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact Adapt Pharma, Inc. at 1-844-ADAPT-11 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See page 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: X/2015

End of Sponsor material

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: **NARCAN® Nasal Spray** Established Name: Naloxone Hydrochloride nasal spray	Acceptable from CMC perspective
Dosage form, route of administration	Dosage: Nasal Spray Route: Nasal	
Controlled drug substance symbol (if applicable)	N/A	

Item	Information Provided in NDA	Reviewer's Assessment
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	NARCAN® nasal spray contains a single dose of 4 mg of Naloxone hydrochloride in 0.1 mL for intranasal use only.	Acceptable from CMC perspective

Conclusion: Acceptable from CMC perspective.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

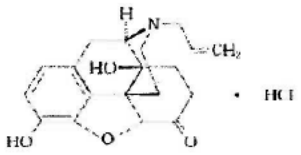
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Nasal Spray	Adequate from CMC Perspective
Strengths: in metric system	4 mg / spray	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	NARCAN® nasal spray is supplied as single dose of 4 mg of naloxone hydrochloride in a 0.1 mL intranasal spray.	

Conclusion: Acceptable from CMC perspective.

#11: Description (21CFR 201.57(c)(12))

Start of Sponsor material:

NARCAN (naloxone hydrochloride) nasal spray is a pre-filled, single dose intranasal spray. (b) (4) Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:



$C_{19}H_{21}NO_4 \cdot HCl$
M.W. 363.84

Naloxone hydrochloride occurs as a white to 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.

Each NARCAN contains a single 4 mg dose of naloxone hydrochloride in a 0.1mL intranasal spray. (b) (4)

Inactive ingredients include benzalkonium chloride (perservative), disodium

ethylenediametetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH, and purified water. The pH range is 3.5 to 5.5.

End of Sponsor material

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Narcan (naloxone Hydrochloride) nasal spray	Adequate from CMC Perspective
Dosage form and route of administration	Nasal Spray, intranasal	
Active moiety expression of strength with equivalence statement for salt (if applicable)	Naloxone Hydrochloride Dihydrate equivalent to 4 mg of Naloxone Hydrochloride	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Benzalkonium chloride (preservative), disodium Ethylenediametetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH, and purified water.	
Statement of being sterile (if applicable)	Not applicable	
Pharmacological/ therapeutic class	opioid antagonist	
Chemical name, structural formula, molecular weight	17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride, $C_{19}H_{21}NO_4 \cdot HCl$ M.W. 363.84	
If radioactive, statement of important nuclear characteristics.	Not applicable	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.	

Conclusion: Acceptable from CMC perspective

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	4 mg /spray	Adequate from CMC Perspective
Available units (e.g., bottles of 100 tablets)	1. Carton containing two blister packages each with a single NARCAN nasal spray. (b) (4)	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A single 4 mg dose of naloxone hydrochloride solution filled into a glass vial fitted with rubber stopper, and place in a container holder and fitted with intranasal spray device for delivering 0.1 mL upon actuation. NDC 69574-353-02	
Special handling (e.g., protect from light, do not freeze)	Do not Freeze.	
Storage conditions	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).	The short term Freeze - thaw study data provided don't support the stated excursions between 4°C and 40°C (between 39°F and 104°F) through the shelf-life of the drug product.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by Adapt Pharma, Inc., Radnor, PA 19087 USA.	Adequate from CMC Perspective

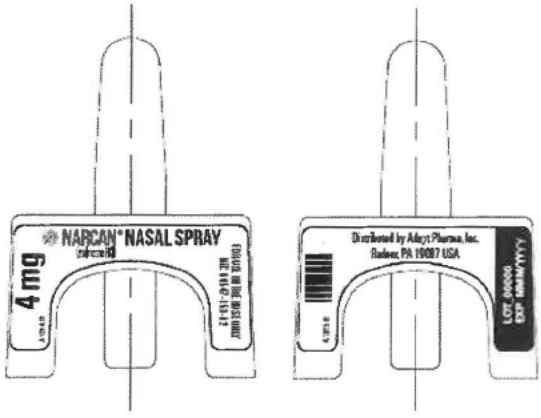
Conclusion:16 Acceptable from CMC perspective, except for the excursions between 4°C and 40°C (between 39°F and 104°F).

2. Labels

1) Immediate Container Label (Double pack)

Start of Sponsor Material

FRONT BACK



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Narcan® Nasal Spray (Naloxone HCl)	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	4 mg	
Net contents (21 CFR 201.51(a))	4 mg	
Lot number per 21 CFR 201.18	LOT_00000	
Expiration date per 21 CFR 201.17	EXP MMM/YYYY	
"Rx only" statement per 21 CFR 201.100(b)(1)	Not present	May be considered for inclusion based on the available space.
Storage (not required)	Not present, too little space to fit the text for storage conditions.	Given on the Blister and outer carton
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 69574-353-02	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	A1015.01 	
Name of manufacturer/distributor	Distributed by Adapt Pharma, Inc. Radnor, PA 19087 USA	
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Label text acceptable from CMC perspective, except for the missing "Rx only" statement that may be considered for inclusion based on availability of the space on container label.

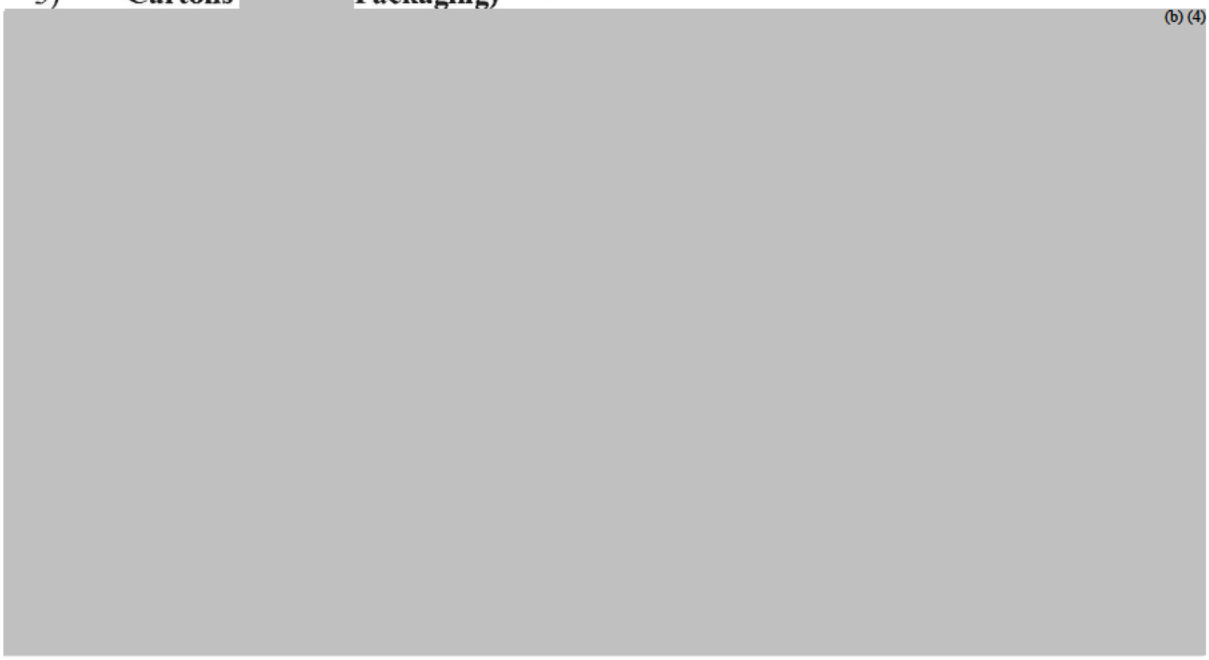
2) **Blister** (b) (4) **Packaging)**

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Acceptable font Size	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	4 mg	
Net contents (21 CFR 201.51(a))	1 spray per unit	
Lot number per 21 CFR 201.18 Expiration date per 21 CFR 201.17	LOT_00000 & EXP MMM/YYYY	
Name of all inactive ingrédients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Not provided.	
Sterility Information (if applicable)	Not Applicable	
"Rx only" statement per 21 CFR 201.100(b)(1)	Included	
Storage Conditions	Store at room temperature between (b) (4) Protect from light	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 69547-353-02	
Bar Code per 21 CFR 201.25(c)(2)**	Present	
Name of manufacturer/distributor	Distributed by Adapt Pharma, Inc. Radnor, PA 19087 USA	
"See package insert for dosage information" (21 CFR 201.55)	"See Enclosed Quick Start Guide"	
"Keep out of reach of children" (optional for Rx, required for OTC)	Optional information Not present	
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For use in the nose only	

3) **Cartons** (b) (4) **Packaging)**

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Acceptable font Size	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	4 mg	
Net contents (21 CFR 201.51(a))	This box contains **two (2)** 4-mg doses of naloxone HCl in 0.1 mL of nasal spray.	
Lot number per 21 CFR 201.18	LOT: XXXXXXXXX	
Expiration date per 21 CFR 201.17	EXP DATE: MMM/YYYY	
Name of all inactive ingrédients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Inactive ingredients information included	
Sterility Information (if applicable)	Not Applicable	
"Rx only" statement per 21 CFR 201.100(b)(1)	Included	
Storage Conditions	STORE AT ROOM TEMPERATURE between (b) (4) DO NOT FREEZE.	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 69547-353-02	
Bar Code per 21 CFR 201.25(c)(2)**	Present	
Name of manufacturer/distributor	ADAPT PHARMA Distributed by Adapt Pharma, Inc. Radnor, PA 19087 USA A1008.01	
"See package insert for dosage information" (21 CFR 201.55)	OPEN HERE FOR QUICK START GUIDE In addition to the statement, a shorter version (quick start guide) was included on the carton.	
"Keep out of reach of children" (optional for Rx, required for OTC)	Optional information Not present	
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For use in the nose only	

Conclusion: Carton text acceptable from CMC perspective.

II. List of Deficiencies Communicated

A. Drug Substance

1. Provide a Certificate of Analysis for the drug substance batches used in the preparation of the drug product clinical batches.

B. Drug Product

1. Provide a specification for total impurities in the drug product release and stability specifications.
2. The chromatograms provided in the validation reports for the HPLC methods are unclear. Provided clear chromatograms to support the validation reports for the HPLC analytical methods
3. Provide information on the solvent used, (purified water (b) (4)) both during product development and in the manufacturing of the individual clinical lots (b) (4)
4. Both Lot number and Batch numbers were used in the executed batch records. In section 3.2.P.8.1 stability summary, in table P.8.1-1 and other places the lot numbers of executed batches were referred to as batch numbers. Provide information on in-house procedures in place for assigning lot number and batch number for drug product(s) and use correct designations in the submission in all places referring to a Lot or Batch number.
5. In section 2.2 Introduction, table 2.2-1, the standards /grade for all the components of drug product were stated as USP and these do not match with what was stated in table P.1.2-1 in section 2.3.P.1. Provide the correct material description, specifications and quantitative composition statements /information for the drug product.
6. In various sections of the submission the amount of Benzalkonium Chloride present in the composition is stated differently, i.e (b) (4) without stating whether it refers to the commonly available (b) (4) Benzalkonium Chloride. Provide the correct description and corresponding percent w/v or milligrams for Benzalkonium Chloride throughout the submission, either as "Benzalkonium Chloride (b) (4) or "Benzalkonium Chloride (b) (4) per EP/NF description.
7. Correct the typo in development report, section 2.3.P: "Experiments 12-17 were designed to study the effect of adding (b) (4)". It should be (b) (4).
8. In section 3.2.P.2.5 Container Closure System of pharmaceutical development, it was mentioned that LC-MS, GC-MS, inductively coupled plasma/optical emission spectroscopy (ICP-OES) and ion Chromatography were used for analysis of organic and inorganic extractables from (b) (4) stoppers. Provide the location in your NDA submission where the final study report(s) for these extraction

results can be found, otherwise submit to the NDA as soon as possible the final extraction report(s) that include details of the analytical methods used, test results of individual extraction studies, and verification / validation of the analytical methods employed in identification of extractables using various solvent indicated, i.e. water, (b) (4) etc.

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

10. Provided Certificates of Analyses (CoAs) for all the incoming materials used in manufacturing of all the Drug Product batches included in the submission, i.e. Drug Substance, Excipients, individual components of the Container Closure System components (b) (4) etc. to section 3.2.R.

11. Provide enlarged and readable chromatograms of standard solutions and drug product samples, preferably samples from forced degradation studies for the assay of naloxone HCL nasal spray, and those generated during validation of the following analytical methods.
(b) (4)

12. Update the relevant sections of the submission to include the newly provided quality information, i.e. Certificates of Analysis for incoming materials (Drug Substance, Excipients etc.) used in the manufacturing of the drug product lots, materials in response to information request.

C. Labeling Information

1. Provide revised label text for the container (UnitDose device) with "Rx only" included.
2. Provide revised text on the carton and blister to contain "Store at room temperature between (b) (4) "Do Not Freeze" "Protect from light". Also update section 16 of the Prescribing Information to reflect these changes to storage conditions.

III. Attachments (Life Cycle management)

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability (DP)	Formulation Raw materials Process parameters (b) (4)	M	(b) (4)	L	Narcan did not exhibit increase in (b) (4) (b) (4) content during release and on (photo) stability testing of DP.
Analytical Methods	Validation Reference standards for each known impurity	M		L	The levels of specified impurities were below the threshold for identification through the end of shelf-life storage.

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature

Venkateswara R. Pavuluri -A (Affiliate)

Digitally signed by Venkateswara R. Pavuluri -A (Affiliate)
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=0011799946, cn=Venkateswara R. Pavuluri -A (Affiliate)
Date: 2015.11.18 15:40:08 -05'00'

B. Endorsement Block

Reviewer Name/Date: [**Venkateswara R. Pavuluri, Nov 1, 2015**]
Secondary Reviewer Name/Date: [**Julia C. Pinto, Nov 1, 2015**]
Project Manager Name/Date:

Julia C. Pinto -S

Digitally signed by Julia C. Pinto -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -S, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.11.18 14:17:07 -05'00'

Updated Labeling & Package Insert: November 17, 2015

The Sponsor requested a change in the excursion temperature statement that is part of the storage statement on carton and PI labels. The requested storage conditions (b) (4) " was changed to " Store at 15-25ºC (59-77ºF), excursions permitted to 4ºC to 40ºC (39-104ºF)". The reason for the change, is that the product is intended to be stored in all police cars and ambulances in the USA. Therefore the product could be stored for long periods of time at temperatures below zero to over 100 ºF. Some limited data is provided in the NDA that includes stability data for 40 ºC storage for 6 months, and freeze – thaw cycling data. It was therefore requested for the Sponsor to agree to a PMC, that includes conducting a full stability study for the drug product stored at 4 ºC and at 40 ºC, for 24 months. In a T-con with the Sponsor, Nov 10, 2015, they agreed to the PMC and provided updated carton labels (shown below) with the revised storage/excursion statement.

(b) (4)

I. Administrative

A. Reviewer's Signature

Venkateswara R. Pavuluri -A (Affiliate)

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Date: 2015.11.18 15:44:07 -05'00'

B. Endorsement Block

Julia C. Pinto -S

Digitally signed by Julia C. Pinto -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -S, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.11.18 14:17:40 -05'00'

Reviewer Name/Date: **Venkateswara R. Pavuluri, Ph.D.; 11/18/2015**

Secondary Reviewer Name/Date: **Julia C. Pinto, Ph.D.; 11/18/2015**

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ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: Release testing includes microbial enumeration and four specified microorganisms including *B. cepacia*. Microbial release testing is done according to USP <61> and <62>.

Test	Method	Acceptance Criteria
Total Aerobic Microbial Count	USP <61> USP <62>	(b) (4) CFU/mL
Total Combined Yeast/Molds Count		CFU/mL
E. coli		Absent
Staphylococcus aureus		
Pseudomonas aeruginosa		
Burkholderia cepacia Complex		

IR #1 Question (August 2015)

3. *Provide the method verification results for Total Aerobic Microbial Count, Total Combined Yeast/Molds Count, specified microorganisms done according to USP <61> and USP <62>.*

Applicant Response: Method Validation Report M-14-078 [The Method Validation Report for Microbial Limits Validation Testing of Naloxone 40mg/mL Nasal Spray (Formula 1044.01)] was added to 3.2.P.5.3. Method (b) (4)-SOP-00686 was provided which describes 1) the microbial limits testing procedure via both the plate and membrane filtration methods; and 2) pathogen screening using specified growth media.

Product lot #14-60112 was tested using the membrane filtration method per USP<61> for *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Aspergillus brasiliensis* and *Candida albicans*. Pathogen screening per USP <62> was performed for *Escherichia coli*, *S. aureus*, *P. aeruginosa* and 3 different strains of *Burkholderia cepacia*. (b) (4)

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contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: There are no excipients of human or animal origin used in the formulation of naloxone hydrochloride nasal spray.

Reviewer's Assessment: Not Applicable

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: There are no excipients of human or animal origin used in the formulation of naloxone hydrochloride nasal spray.

Reviewer's Assessment: Not Applicable

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Following a review of the application and IR response received, there are no significant, outstanding microbiological risks that prevent approval of this application. NDA 208411 is found to be acceptable.

Christina Capacci-Daniel, PhD - 14Oct2015
Consumer Safety Officer, OPQ/OPF/DIA/IAB2

Christina A. Capacci-daniel -S
Digitally signed by Christina A. Capacci-daniel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001237147, cn=Christina A. Capacci-daniel -S
Date: 2015.11.18 14:24:19 -05'00'

Secondary Review Comments and Concurrence:

I concur.

Erika Pfeiler, Ph.D.
Quality Assessment Lead (Acting)
OPQ/OPF/DMA
15 October 2015

Erika A. Pfeiler -S
Digitally signed by Erika A. Pfeiler -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000396533, cn=Erika A. Pfeiler -S
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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208411	**Submission Type: Fast Track**	**Established/Proper Name: Naloxone Hydrochloride**
Applicant: Adapt Pharma	**Letter Date: July 20, 2015**	**Dosage Form: Intranasal**
Chemical Type:	**Stamp Date: July 20, 2015**	**Strength: 4 mg/100ul**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		This NDA is filable from the CMC standpoint. No Biopharmaceutics review is needed since the product is a spray, and no biowaiver is requested.
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			See IR Letter Sent to the Applicant Dated August 21, 2015 (Appendix 1)

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	x	
2.	Botanical[1]	☐	X	
3.	Naturally-derived Product	☐	X	
4.	Narrow Therapeutic Index Drug	☐	X	
5.	PET Drug	☐	X	
6.	PEPFAR Drug	☐	X	
7.	Sterile Drug Product	☐	X	
8.	Transdermal[1]	☐	X	
9.	Pediatric form/dose[1]	☐	X	
10.	Locally acting drug[1]	☐	x	
11.	Lyophilized product[1]	☐	x	
12.	First generic[1]	☐	x	
13.	Solid dispersion product[1]	☐	x	
14.	Oral disintegrating tablet[1]	☐	x	
15.	Modified release product[1]	☐	x	
16.	Liposome product[1]	☐	x	
17.	Biosimiliar product[1]	☐	x	
18.	Combination Product _____	☐	x	
19.	Other_____	x	☐	Fast Track Designation: Intranasal naloxone for treatment of opiate overdose.

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Regulatory Considerations					
20.	USAN Name Assigned		☐	☐	
21.	End of Phase II/Pre-NDA Agreements		☐	☐	
22.	SPOTS (Special Products On-line Tracking System)		☐	☐	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☐	
24.	Comparability Protocol(s)[2]		☐	☐	
25.	Other		☐	☐	
Quality Considerations					
26.	Drug Substance Overage		☐	☐	
27.	Design Space	Formulation	☐	☐	
28.		Process	☐	☐	
29.		Analytical Methods	☐	☐	
30.		Other	☐	☐	
31.	Real Time Release Testing (RTRT)		☐	☐	
32.	Parametric Release in lieu of Sterility Testing		☐	☐	
33.	Alternative Microbiological Test Methods		☐	☐	
34.	Process Analytical Technology[1]		☐	☐	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	☐	
36.		Excipients	☐	☐	
37.		Microbial	☐	☐	
38.	Unique analytical methodology[1]		☐	☐	
39.	Excipients of Human or Animal Origin		☐	☐	
40.	Novel Excipients		☐	☐	
41.	Nanomaterials[1]		☐	☐	
42.	Hold Times Exceeding 30 Days		☐	☐	
43.	Genotoxic Impurities or Structural Alerts		☐	☐	
44.	Continuous Manufacturing		☐	☐	
45.	Other unique manufacturing process[1]		☐	☐	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☐	
47.	New delivery system or dosage form[1]		☐	☐	
48.	Novel BE study designs		☐	☐	
49.	New product design[1]		☐	☐	
50.	Other		☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	x	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance	x	☐	☐	A rolling submission

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C. FILING CONSIDERATIONS					
	❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols				
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	x	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	x	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	x	☐	☐	Referenced to DMF (b) (4)
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture		x	☐	Referenced to DMF (b) (4)

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FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ❑ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product ○ Includes production data on drug product	x	☐	☐	

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FILING REVIEW

C. FILING CONSIDERATIONS					
	manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	x	No Biopharmaceutics Review is required. The product is a spray and the Sponsor is not requesting a biowaiver.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	x	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	x	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	x	
12.	For an extended release dosage form, is there enough information to assess the extended release	☐	☐	x	

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FILING REVIEW

C. FILING CONSIDERATIONS					
	designation claim as per the CFR?				
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	x	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	x	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	x	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			x	

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FILING REVIEW

Risk Assessment Table

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, Stability (DP)	Formulaion Raw materials Process parameters (b) (4)	1	2	Release (1) Stability (3)	Release (2) Stability (6) medium	The DP has a 2 year expiry. Possible (b) (4) formation over time.
API Stability	Formulation Raw materials Process parameters (b) (4)	3	2	4	36(medium)	API stable at 25C for 2 years
Process DP	Dissolution of excipients Fill of vials Hold time Assemble of device	3	3	4	36 (medium)	Fill is under (b) (4) Hold time and subsequent device assembly are critical to avoid product degradation and optimal dose delivery
Device Unit Spray	Device assembly Fill Dose delivery	1	2	4	Release (2) Stability (6) low	Unit dose device is a simple spray with a single dose to the nostril. Proper assembly of the vial and device is essential to ensure optimal dose delivery and function of the spray device
Analytical Methods	Validation Reference standards for each known impurity	3	3	4	36 (medium)	Methods need to be fully validated for each impurity and the product, using reference standards.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Appendix I

NDA 208411 IR #1

1. Provide a specification for total impurities in the drug product release and stability specifications.
2. Provide a Certificate of Analysis for the drug substance batches used in the preparation of the drug product clinical batches.
3. The chromatograms provided in the validation reports for the HPLC methods, are unclear. Provided clear chromatograms to support the validation reports for the HPLC analytical methods
4. Provide information on the solvent used, (purified water (b) (4)) both during product development and in manufacturing of the individual clinical lots (b) (4)

5. Both Lot number and Batch numbers were used in the executed batch records. In section 3.2.P.8.1 stability summary, in table P.8.1-1 and other places the lot numbers of executed batches were referred as batch numbers. Provide information on in-house procedures in place for assigning lot number and batch number for drug product(s) and use correct designations in the submission at all places, referring to a lot or Batch numbers

6. In section 2.2 Introduction, table2.2-1 the standards / grade for all the components of drug product were stated as USP and these doesn't match with what was stated in table P.1.2-1 in section 2.3.P.1. Provide correct material description, specifications and quantitative composition statements / information for the drug product.

7. In various sections of the submission the amount of Benzalkonium Chloride present in the composition was stated differently, i.e. (b) (4) without stating whether it refers to the commonly available (b) (4) Benzalkonium Chloride. Provide correct description and corresponding percent w/v or milligrams for Benxalkonium Chloride throughout the submission, either as "Benzalkonium Chloride (b) (4) or "Benzalkonium Chloride (b) (4) per EP/NF description.

8. Correction of typo in development report, section 2.3.P "Experiments 12-17 were designed to study the effect of adding (b) (4). It's should be (b) (4).

9. Formulation Development Study 1 shows that the formulation is stable with EDTA only when protected from light. Provide a manufacturing risk assessment for potential light degradation and describe any manufacturing process steps taken to protect the bulk solution and filled vials from light.

10. Provide data to support that the [redacted] (b) (4)

11. To the proposed Master Batch Record, add visual inspection in-process controls to confirm the dissolution of each component as described in 3.2.P.3.3.2, or provide a rationale based on development studies for not including these in-process controls.

12. Update the Master Production Record to document the results of the [redacted] (b) (4) test.

13. Provide a statement about [redacted] (b) (4) the bulk solution.

14. Indicate any [redacted] (b) (4)

15. Elaborate on the assembled unit inspection criteria, [redacted] (b) (4)

16. Module 3.2.P.3.3.1.1 describes several [redacted] (b) (4)

17. Provide the method verification results for the Total Aerobic Microbial Count, Total Combined Yeast/Molds Count, and specified microganisms assays done according with USP <61> and USP <62>.

18. [redacted] (b) (4)

[redacted] (b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

(b) (4)

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FILING REVIEW

{See appended electronic signature page}

NAME: Julia Pinto, Ph.D.

Acting Branch Chief

OPQ/ONDP/DNDP/Branch IV

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.08.18 19:26:37 -04'00'

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Center for Drug Evaluation and Research/OPQ/OPF

DATE:	October 13, 2015
TO:	Julia Pinto, PhD, CDER/OPQ/ONDP Julia.Pinto@fda.hhs.gov Eric Duffy, PhD, CDER/OPQ/ONDP Eric.Duffy@fda.hhs.gov Office of Combination Products at combination@fda.gov
Through:	For Cisco Vicenty, Chief, Branch, DMQ, OC, CDRH, OMPT

From:	Juandria Williams, PhD, CDER/OPQ/OPF
Applicant:	Adapt Pharma Operations Limited 45 Fitzwilliam Square Dublin 2, Ireland
Application:	NDA 208411
Product Name:	Naloxone Hydrochloride Nasal Spray
Consult Instructions:	To evaluate the relevant device manufacturers and recommend on their acceptability to support NDA 208411

Inspection Needed: No

Documentation Review: No additional information required

Final Recommendation: Approval

The Office of Process and Facilities in CDER, in consultation with the Office of Compliance in CDRH, evaluated the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 208411.

PRODUCT DESCRIPTION

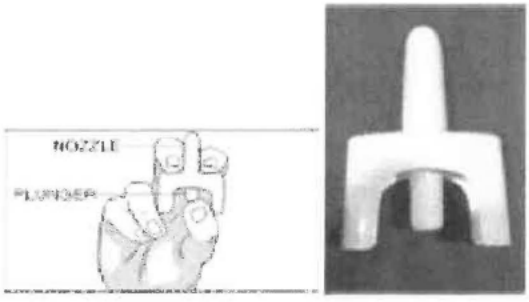
The NARCAN (naloxone hydrochloride) nasal spray is an aqueous solution presented in a stoppered glass vial mounted into a unit-dose nasal spray device. Each delivered dose contains (b) (4) 4 mg naloxone (b) (4) The finished combination product is intended for immediate administration as emergency therapy in settings where opioids may be present.

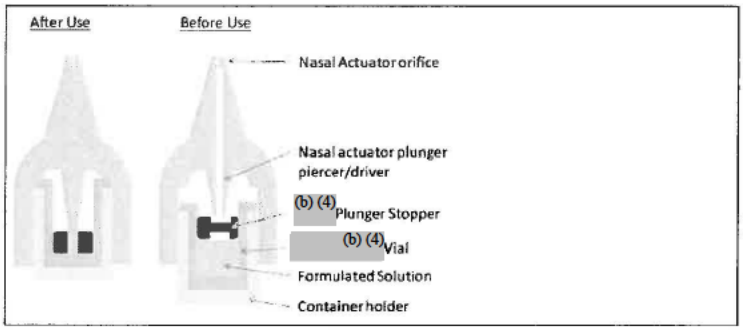
Filled drug product vials are assembled into a unit dose device constituent part comprising a nasal actuator and container holder. When the patient actuates the unit by pressing the base of the actuator with their thumb and pressing their fingers against, the actuator "wings", the nasal actuator pierces the narrowed section of the plunger stopper and the liquid is propelled through the orifice tip and exists as a fine spray of droplets.

The finished combination product is based on an injectable formulation approved under NDA 016636. Adapt developed the current intranasal formulation based on QbD principles and is suitable for clinical and at-home use. Adapt based the initial formulation on that used in the (b) (4) pre-filled syringe and nasal atomizer kit product.

The finished combination product is manufactured at (b) (4).

Naloxone Nasal Spray with Device Components





REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR Part 4:

Adapt Pharma Operations Limited
45 Fitzwilliam Square
Dublin 2, Ireland

The firm designed, developed, and currently owns the rights to, the Naloxone HCL Nasal Spray combination product. The firm does not appear to have FDA inspectional history. They did provide a summary description of how their design process fulfills the requirements for 21 CFR 820.30 (see "Documentation Review" below). A pre-approval inspection is not required to approve this NDA; however, a post-approval inspection is recommended.

(b) (4)

The firm proposes to formulate, fill, and assemble the finished combination product. The firm is primarily a drug product manufacturer; however, a 2014 pre-approval inspection of a finished combination product resulted in an NAI, as well as GMP inspectional coverage. While the device constituent parts were not specifically covered under an applicable device PAC, it appears that the drug product GMPS similar to relevant device GMPs were considered adequate. Additionally, the last two surveillance inspections found the facility acceptable.

A pre-approval inspection is not required to approve this NDA; however a post-approval inspection covering applicable Medical Device Regulations is recommended.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

(b) (4) is responsible for complying with this regulation. (b) (4) Quality organization is independent of the Operations organization, with the heads of both reporting to the (b) (4) President. The firm holds site management performance meetings on a monthly basis to ensure executive management is kept apprised of all aspects of the business. A Quality Metrics meeting is held at least quarterly per their Site Quality Management Review SOP.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

Adapt Pharma is responsible for implementing design control activities. Adapt adopts the (b) (4) principle as described in the CDRH Design Control guidance for Medical Device Manufacturers.

The firm received design input from clinicians, pharmacologists, and other subject matter experts who were engaged with Adapt's Head of Technical Operations, responsible for development, manufacturing, and supply of products. The proposed NARCAN Naloxone HCL Nasal Spray was selected after risk-based consideration of other available technologies. The product's critical attributes were identified, resulting in an updated development plan to include risk mitigation of new issues. Design verification analysis was performed by Adapt, subject matter experts, and supply partners, and reviewed by the design review team who ultimately updated and approved the development plan. As a part of the development plan, the individual components, sub-assemblies, formulation, and finished product were reviewed to develop a Quality and Technical Agreement (QTA) and Quality Plan for each component and sub-assembly. The QTA outlines requirements for the acceptance procedures, specifications, and change control for the components, sub-assemblies, as well as materials used in the manufacture of the finished product.

Design verification analyses was reviewed and approved during the design reviews and quality reviews with supply partners. The development plan was subsequently approved to complete the pivotal clinical studies.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

(b)(4) evaluates suppliers, as specified by the client, according to product characterstics and delivery system attributes. (b)(4) purchasing department is required to maintain contracts with suppliers to ensure quality and change notification requirements. The suppliers are monitored via an annual risk assessment process based on quality performance as per their SOP "Risk-based Selection of Raw Material Vendor Audits". Adapt has an SOP that outlines the evaluation, qualification, and oversight of all contract vendors associated with the manufacture of NARCAN HCL Nasal Spray.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The (b)(4) system is managed through Trackwise. Their SOPs '(b)(4)Quality Deviation, Investigation, and CAPA Procedure", and "TrackWise Corrective Action and Preventive Action Workflow" provides details of CAPA initiation, implementation, and effectiveness.

In general, a CAPA is assigned to the responsible department with a description of the overall actions required for correction and prevention. A summary of results are documented in Trackwise followed by a review of the CAPA to ensure all actions are complete. The complete CAPA is then routed for review and approval by Adapt. The copy of the approval is forwarded to (b)(4) for final approval.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170
Installation is not required for this combination product.

Servicing, 21 CFR 820.200
Installation is not required for this combination product.

MANUFACTURING

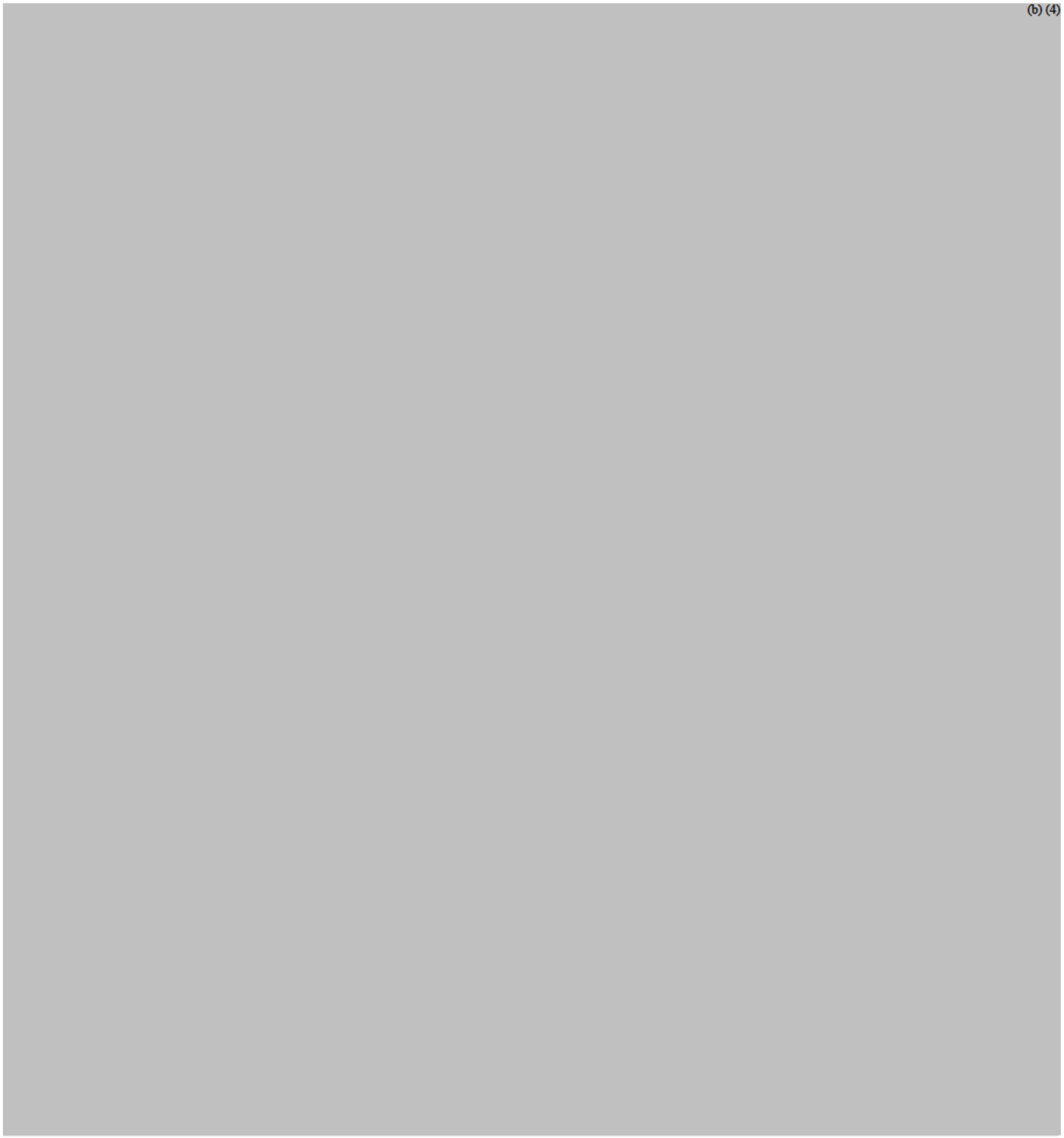
Production and Process Controls

(b) (4) proposes to implement controls of critical steps including the formulation, the fill, and the final assembly of the finished product. A table of the steps and associated in-process controls with acceptance criteria is provided below.

Step	In-process Control	Acceptance Criteria
(b) (4)		

Production Flow

(b) (4)



Acceptance Activities

The QTA outlines Adapt's requirements for the acceptance procedures and specifications for each of the finished product components and sub-assemblies. (b) (4) performs the acceptance activities. Testing and test limits to be met for (b) (4) are defined in Adapt's specifications as described in the application.

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The Office of Process and Facilities, in consultation with CDRH, has completed the evaluation of application NDA 204811 and recommends the following:

1. Approval of the application
2. Post-approval inspection coverage of the proposed product at the following firms:
    a. Adapt Pharma Operations Limited
    b. (b) (4)

Juandria Williams, PhD
Acting Quality Assessment Lead
CDER/OPQ/OPF

Prepared: JVWilliams: 10/13/2015

Reviewed: VVerna: 10/14/2015

NDA 208411