CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217722Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 217722 Executive Summary

1. Application/Product Information

NDA Number.	NDA 217722
Applicant Name	Harm Reduction Therapeutics (HRT), Inc.
Drug Product Name	RiVive (naloxone hydrochloride)
Dosage Form.	Spray
Proposed Strength(s)	3 mg/0.1 mL
Route of Administration	Nasal
Maximum Daily Dose	6 mg
Rx/OTC Dispensed	OTC
Proposed Indication	Emergency treatment for opioid overdose
Drug Product Description	RiVive, naloxone hydrochloride 3 mg/0.1 mL nasal spray is a new pharmaceutical formulation of the active substance naloxone. RiVive is designed to be an over the counter (OTC) naloxone drug-device combination product. The drug product portion is an aqueous, non-sterile, (b) (4) nasal solution. The product is a single-use, disposable device intended to administer a unit dose of naloxone to the intranasal (IN) cavity of a patient.
Co-packaged product information	N/A
Device information:	The combination product employs the (b) (4) ((b) (4) drug delivery device designed and manufactured by (b) (4) This delivery device is a single-use, disposable device intended to administer a unit dose of naloxone to the IN cavity. The combination product is composed of a filled vial, a plunger/stopper, a container holder, and the actuator subassembly

Storage Temperature/ Conditions	25°C/60%RH; (b) (4) .		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sithamalli Chandramouli, Ph.D.	Su Tran, Ph.D.
	Drug Product/ Labeling	Elise Luong, Ph.D.	Swapan De, Ph.D. Danae Christodoulou, Ph.D.
	Manufacturing	Xueli Zhu. Ph.D.	Erin Kim, Ph.D.
	Biopharmaceutics	N/A	
	Microbiology	Daniel Schu, Ph.D.	Yeissa ChabrierRosello, Ph.D.
	Other (specify):	None	
	RBPM	Teshara Bouie	
	ATL	Swapan K De, Ph.D.	
Consults	CDRH: Dunya Karimi, Ph.D. OTR: Michelle Stafford, Ph. D.		

2. Final Overall Recommendation -

Approval

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 217722 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a

quality perspective. The drug product has been granted a shelf life of 36 months in the proposed container closure configurations.

Critical CMC issues resolved during the review are briefly described below.

Drug substance

The drug substance supplier, [redacted] (b) (4) he issue was resolved based on HRT's response that prior to cessation of manufacturing activities at [redacted] (b) (4) HRT secured enough naloxone hydrochloride to support the commercial manufacture of the drug product for several years. This drug substance is in inventory at the drug product manufacturer, [redacted] (b) (4) is responsible for continuing GMP activities (e.g., retest testing for the active pharmaceutical ingredient).

[redacted] (b) (4)

Drug product

RiVive (naloxone hydrochloride 3 mg/0.1 mL) nasal spray is proposed as a nonprescription naloxone product. It is a drug-device combination product with a new pharmaceutical formulation of the active substance naloxone. [redacted] (b) (4) The product is a single-use, disposable device intended to administer a unit dose of naloxone to the intranasal cavity of a patient. The primary container closure consists of a glass vial and stopper designed to contain the drug product in the [redacted] (b) (4) .

Components and composition, manufacturing controls, drug product critical quality attributes and in-process controls, microbiological controls and facilities sections of the application were reviewed, and they are adequate from the CMC perspective. Major issues encountered during review are discussed below.

The microbiological controls section of the drug product required significant communication with the Applicant throughout the review cycle including many rounds of information requests and teleconferences (dated January 23, 2023, and February 1, 2023) related to microbiological quality attributes of the subject drug product, associated microbiological controls, and endpoint testing for the drug product manufacturing process. The microbiology review was ultimately finalized following a review of an amendment dated May 5, 2023, covering results from the FDA recommended growth promotion study of the formulation. Submitted results indicate that the drug product does not support microbial growth.

The device part of the drug product includes a [redacted] drug delivery device designed and manufactured by [redacted] All device related information including device description, labeling, design controls, risk analysis, design verification, and facilities and quality systems are performed by CDRH team. It was concluded that all data provided in the review demonstrate adequate and reliable performance of the device to a 99.999% reliability, which is consistent with what is expected of emergency use devices. Stability data demonstrate adequate essential parameters performance up to 36 months.

Granted expiry: 36 months when stored at 25°C/60%RH, is based on 24 months real time stability data and statistical analysis evaluation per ICH Q1E. OPQ statistical team confirmed the applicant's analysis of trending attributes [redacted] unspecified impurities and total degradation products.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comparability Protocols (PACMP): No

Additional Lifecycle Comments:

[redacted]

The applicant will consider FDA's recommendation [redacted]

Based on statistical analysis, 36-month expiry is granted for the drug product when stored at 25°C/60%RH. [redacted]

(b) (4)

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental Analysis (EA)

In accordance with 21 CFR 25.31(b), Harm Reduction Therapeutics claims a categorical exclusion from the requirement to prepare an Environmental Assessment as the concentration of Naloxone HCl that will be utilized under this NDA for commercialization is not expected to exceed the threshold of 1 μg/L (i.e., 1 ppb).

To Harm Reduction Therapeutics' knowledge there are no extraordinary circumstances that might cause this action to have a signification effect on the quality of the environment.

Assessment: ***Adequate from a CMC perspective.***

To the best knowledge of the applicant, no extraordinary circumstances exist associated with the proposed actions. The EA review team will document its review under the OND's Integrated Review Process (if applicable).

Primary Environmental Assessor Name and Date: Elise Luong, Ph.D.; 06/13/2023.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Swapan De, Ph.D.; 06/13/2023 I concur with the reviewer's assessment.

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Labeling data from the approved product will be adopted for the DFL label (OTC Use). Below is evaluation of the data for the prescription product.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Rivive™	Propriety name was conditional approved by DMEPA on 05/05/2020 for OTC use.
Established name(s)	Naloxone HCl	Adequate
Route(s) of administration	intranasal	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Naloxone HCl nasal spray solution 3 mg per spray of 0.1 mL	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	The drug product is ready to use.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Single use nasal spray solution	Adequate
Strength(s) in metric system	Naloxone HCl 3 mg per 0.1 mL dose	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Section 3.2.P.1	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name Established name(s)	Rivive™ Naloxone HCl	Propriety name was conditional approved by DMEPA on 05/05/20 for OTC use.
Dosage form(s) and route(s) of administration	Single use nasal spray solution	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names	Trisodium citrate dihydrate Sodium chloride Hydrochloric acid Sodium hydroxide (b) (4) Purified water	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The drug product does not contain alcohol	N/A
Statement of being sterile (if applicable)	This is a non-sterile product	N/A
Pharmacological/ therapeutic class	Inverse agonist for opioid receptors	Adequate

Chemical name, structural formula, molecular weight	(5R,9R,13S,14S)-17-(prop-2enyl)-3,14-dihydroxy-4,5-epoxymorphinan-6-one hydrochloride Molecular weight: 399.87 $C_{19}H_{21}NO_4 \bullet 2H_2O$	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	• White to slightly off-white powder • Freely soluble in water, soluble in ethanol, practically insoluble in toluene	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	There is no misleading statement on the labels	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Single use nasal spray solution	Adequate
Strength(s) in metric system	Naloxone HCl 3 mg/0.1 mL/single use dose	Adequate
Available units (e.g., bottles of 100 tablets)	(b) (4) mL fill vial for 0.1 mL per actuation, 1 actuation per device	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear, colorless to pale yellow liquid	Adequate. The description has been provided in the NDA.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.)	Store between at 20°-25°C (68° -77°F)	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store between at 20°-25°C (68° -77°F)	The storage condition is supported by 24 months long-term stability data.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenteral, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.
Please include your comments about other sections of labeling if they contain product quality information.

Consumer Information Quick Start Guide

(b) (4)

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1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Harm Reduction Therapeutics, Inc. Bethesda, MD 20814	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

None.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Representative examples of a proposed containers)

(b) (4)

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Rivive	Adequate
Dosage strength	Naloxone HCl 3.0 mg/0.1 mL per spray	Adequate
Route of administration	Single use nasal spray solution	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g., tablet count)	2 nasal sprays per carton	Adequate
"Rx only" displayed on the principal display	N/A (This is OTC product)	N/A
NDC number	Labels contain space for NDC number	Adequate
Lot number and expiration date	Label does not show allocated space for lot number and expiration date	CMC comment was conveyed to the labeling team.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	CMC comment was conveyed to the labeling team, requesting the applicant to add 'between 20°-25°C (68° to 77°F)

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The product does not contain alcohol.	Adequate
Bar code	Labels have space for bar code	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Harm Reduction Therapeutics, Inc.	Adequate
Medication Guide (if applicable)	Labels have user quick guide	Adequate
No text on Ferrule and Cap Overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	There is no USP monograph for the drug product	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling:

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective except the following:

- *The container label does not have space allocated for lot number and expiration date.*
- *The container label does not spell out the storage temperature in degree. For example, stored between 20°-25°C (68° to 77°F).*

CMC comments have been conveyed to the labeling review team. Labeling will be finalized through OND during labeling negotiations with the applicant.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

None.

Primary Labeling Assessor Name and Date: Elise Luong, Ph.D., 06/13/2023. Secondary Assessor Name and Date (and Secondary Summary, as needed): Swapan De, Ph.D., 06/13/2023.

Elise Luong

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Date: 6/13/2023 09:41:56AM
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Swapan De

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GUID: 508da7220002a114329c9e07775b6e02

Danae Christodoulou

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the NDA IQA Guide

Product Information	
NDA Number	217722
Assessment Cycle Number	1
Drug Product Name/ Strength	Naloxone hydrochloride (Proposed Proprietary Name: RiVive)/3 mg/0.1 mL
Route of Administration	Intranasal
Applicant Name	Harm Reduction Therapeutics, Inc.
Therapeutic Classification/ OND Division	Opiate antagonist/DNDP
Manufacturing Site	(b) (4)
Method of Sterilization	N/A. The drug product is non-sterile.

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Seq 0002	10/28/2022
Seq 0007	12/12/2022
Seq 0009	01/10/2023
Seq 0013	02/06/2023
Seq 0018	02/17/2023
Seq 0019	03/02/2023
Seq 0021	03/08/2023
Seq 0023	03/21/2023
Seq 0026	05/05/2023
Seq 0028	05/18/2023
Seq 0030	05/26/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A.

Remarks: The subject combination drug/device product is indicated for the emergency treatment of opioid overdose. The product is a single use, disposable device intended to administer a single, fixed dose of naloxone to the intranasal cavity of a patient. The primary container closure consists of a glass vial and stopper designed to contain the drug product in the (b) (4)

(b) (4) The drug product portion is an aqueous, non-sterile, (b) (4) nasal solution. The applicant references Narcan (naloxone hydrochloride Injection 0.4 mg/mL) as the RLD.

The combination drug/device product is proposed for over the counter use. The application was granted priority review designation and was originally given a 6 month review timeline (PDUFA date of 04/28/2023). However, on 17 February 2023 (Seq 0017), the Agency received a response to an 08 February 2023 Information Request (IR) regarding a CDRH consult for the application, which constituted a major amendment to the application. Therefore, the goal date was extended by three months to provide time for a full review of the submission. The extended user fee goal date was 28 July 2023.

The assessment of the application required significant communication with the applicant throughout the review cycle including many rounds of information requests and teleconferences (dated 23 January 2023 and 01 February 2023) related to microbiological quality attributes of the subject drug product and associated microbiological controls and end point testing for the drug product manufacturing process. Many of these communications related to the lack of data from a growth promotion study in support of the applicant's claim that the subject drug product did not having microbial growth promotion capabilities. These communications also included requests by the applicant during the review cycle on proposed protocols for development studies including a growth promotion study for the subject drug product. Ultimately, the applicant provided data in the 05 May 2023 (Seq 0026) amendment for a growth promotion study that demonstrated the drug product did not support microbial growth. Further details regarding each of these communications with the applicant are documented throughout the review below.

The submission **is recommended** for approval on the basis of product quality microbiology.

Concise Description of Outstanding Issues: N/A.

Supporting Documents: N/A.

S DRUG SUBSTANCE- N/A. The subject drug product is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- Description of drug product –
  (See Seq 0002, Section 3.2.P.1, *Description and Composition of the Drug Product* document)

  The subject drug product is an aqueous, non-sterile, (b) (4), nasal solution for single dose administration.

- Drug product composition –
  (See Seq 0002, Section 3.2.P.1, *Description and Composition of the Drug Product* document)

  The following table was provided for the composition of Naloxone HCL Nasal Spray 3 mg.

Table 1: Composition of Naloxone HCl Nasal Spray 3 mg

Component	Quality standard	Quantity per dose (mg) #	Quantity per vial (mg) §	Function
Naloxone hydrochloride dihydrate	USP	(b) (4)		Active ingredient
Trisodium Citrate dihydrate	USP			(b) (4)
Sodium chloride	USP			
Hydrochloric acid	NF			
Sodium hydroxide	NF			
(b) (4)				
Purified water	USP			
(b) (4)				

- Description of container closure system-
  (Seq 0002, Section 3.2.P.7, *Container Closure System* document; Section 3.2.R, *Regional Information* document)

  Primary container closure

  The drug primary container-closure system (CCS) is comprised of a (b) (4) glass vial sealed with a (b) (4) stopper/plunger. The applicant states the glass vial and stopper are designed to contain the drug product in the nasal spray drug delivery

device until the device is actuated by the user. The following table was provided for a summary of the drug primary CCS.

Component	Description	Supplier	Formulation	Conformity	Drug Product Contact	References
Unit Dose Vial	[redacted]	[redacted]	[redacted]	(b) (4)	Yes	Figure 1: Technical Drawing Figure 2: Sample CoC
Plunger/ stopper	[redacted]	[redacted]	[redacted]	[redacted]	Yes	Figure 3: Technical Drawing Figure 4: Sample CoC

Nasal Spray Drug Delivery Device

The [redacted] (b) (4) is a single use, disposable device intended to administer a single, fixed dose of naloxone to the intranasal cavity of a patient. The applicant states the nasal drug delivery device is combined with the naloxone HCl drug primary CCS as a single integral product, and thus, is considered a drug/device combination product as per 21 CFR 3.2(e)(1). The applicant states the design features of the device prevent partial dosing once device actuation is initiated. Additionally, the applicant states the [redacted] (b) (4) delivery device platform technology has been proven as safe, effective, and reliable during the 30+ years it has been available on the US market. [redacted] (b) (4)

(b) (4)

The following figure was provided for a diagram of the assembled combination product.

The (b) (4) is supplied by (b) (4) as (b) (4)

figure was provided for a representative photo of the finished product configuration.

Figure 1: Representative Photo of Finished Product Configuration

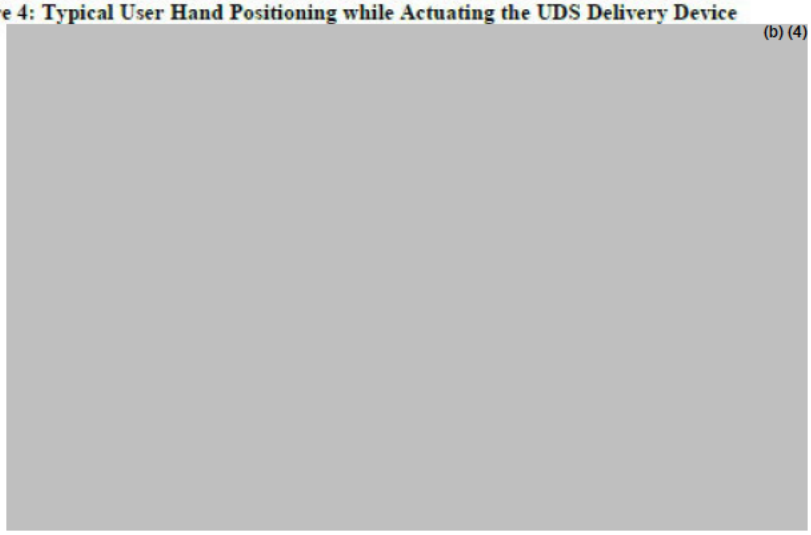
(b) (4)

Principles of Operation

The Naloxone HCl Nasal Spray 3 mg combination product contains (b) (4) microliters of naloxone HCl solution (30 mg/mL). Upon actuation of the nasal spray device, 100 microliters are delivered to the nasal cavity of the patient. To actuate the device, the user places their fore and middle finger on the finger flange of the device, and their thumb on the end of the container holder. The following figure was provided for a depiction of the typical user hand positioning while actuating the (b) (4) delivery device.

Figure 4: Typical User Hand Positioning while Actuating the UDS Delivery Device

(b) (4)



The user pushes upwards on the container holder with their thumb and against the counter-pressure from their fingers. (b) (4)

(b) (4) The following figure was provided for principles of operation/device actuation.

Figure 5: Principles of Operation / Device Actuation

(b) (4)

Prior to actuation, the drug product is contained within the primary container-closure system (i.e., the glass vial and stopper). Upon actuation, the drug product passes through the (b) (4) as it exits into the patient's intranasal cavity. Thus, the (b) (4) all transiently interact with the drug product during actuation of the drug product.

Assessment: *Adequate*
The applicant provided an adequate description of the drug product composition and the container-closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

- Container/Closure and Package Integrity- **N/A.**

Assessment: N/A. The subject drug product is labeled as non-sterile.

(b) (4)

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