CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215457Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215457
Assessment 1

Drug Product Name	Naloxone Auto-Injector (NAI) (a single-use auto-injector that delivers naloxone hydrochloride (HCl) via subcutaneous or intramuscular injection)
Dosage Form	solution
Strength	10 mg (25 mg/mL)
Route of Administration	subcutaneous or intramuscular injection
Rx/OTC Dispensed	Rx
Applicant	kaleo, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	31 Aug 21	All, original submission
Supporting document 4; eCTD 0004	28 Oct 21	Facilities
Supporting document 8; eCTD 0008	24 Nov 21	Facilities
Supporting document 10; eCTD 0010	16 Dec 21	Process/facilities
Supporting document 12; eCTD 0012	4 Jan 22	Microbiology
Supporting document 13; eCTD 0013	7 Jan 22	Drug product
Supporting document 17; eCTD 0017	21 Jan 22	CDRH, drug product, microbiology
Supporting document 19; eCTD 0019	28 Jan 22	Drug product
Supporting document 20; eCTD 0020	31 Jan 22	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Jeff Medwid	Donna Christner
Drug Product	Renish Delvadia	Julia Pinto
Manufacturing	Jonathan Swoboda	Lane Christensen
Microbiology	Eric Adeeku	Paul Dexter
Biopharmaceutics	Assad Noory	Hansong Chen
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Renish Delvadia	Julia Pinto

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	1	9 Nov 21 by Jeff Medwid	
	III			4		
	III			4		
	III			4		
	V			4		
	V			4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	016636	RLD - Narcan
IND	112292	
NDA	205787	Evzio (autoinjector) 0.4 mg/ 0.4 mL (discontinued)
NDA	209862	Evzio (autoinjector) 2 mg/ 0.4 mL (discontinued)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				Sreya Tarafdar
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this application based on drug substance, drug product, manufacturing and microbiology reviews. There will be postmarketing requirements from the drug product reviewer. See the drug product summary below for details.

The proposed shelf life of 24 months is acceptable when stored at controlled room temperature 15°C - 25°C (59°F - 77°F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Naloxone Auto-Injector (NAI) is a single-use auto-injector that delivers naloxone hydrochloride (HCl) via subcutaneous or intramuscular injection. NAI is a drug-device combination product containing a prefilled naloxone HCl Drug Constituent Component.

The Drug Constituent Component of NAI is a parenteral solution formulation (b) (4) glass cartridge and enclosed by an elastomeric plunger and elastomeric lined crimp cap (i.e., primary container closure).
The Device Constituent Component of NAI is a (b) (4) needle-based system that delivers the prescribed dose of naloxone HCl into the user. When activated, NAI will inject a single dose of naloxone HCl. NAI is designed to be a single use device, so any residual parenteral formulation remaining in the device after injection of the dose cannot be utilized.

The proposed shelf life of 24 months is acceptable when stored at controlled room temperature 15°C - 25°C (59°F - 77°F).

Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	acute
Maximum Daily Dose	10 mg
Alternative Methods of Administration	Rx

B. Quality Assessment Overview

Drug Substance: Adequate

The majority of information on Naloxone HCl was submitted in DMF (b) (4) The most recent review was performed by Jeff Medwid and approved by Donna Christner on November 8, 2021. The stability data support a retest period (b) (4) when stored at (b) (4) °C, (b) (4) %.

Drug Product: Adequate

The Applicant has provided 18 months of long-term (25± 2°C/60 ± 5% RH) and 6 months of accelerated (40 ± 2°C/75 ± 5% RH) stability data for two registration batches of drug cartridges, and 12-months of long-term and 6 months of accelerated stability data for one finished auto-injector drug product batch. Additional supportive 18 months of cold storage (2-8°C) stability data are provided for the three registration stability batches.

Unspecified impurities exceeded the ICH identification threshold of 0.2% were observed in long-term and accelerated stability samples at relative retention time (RRTs) of (b) (4) The Applicant has provided information that indicate that these unknown impurities (b) (4) Per the recommendation from the nonclinical division (Drs. Carlic Huynh, Dan Mellon, and Newton Woo), the proposed specification of (b) (4) % for the three unknown impurities is deemed acceptable because the impurities (b) (4)

The available 18 months of long-term and 6-months of accelerated registration stability data remained within specification. No stability trends, other than those related to impurities, were observed.
The Applicant has provided temperature cycling data to support a short-term unintentional temperature variation that might occur during shipping.
Overall, the submitted data supports the shelf-life of 24 months for the proposed drug product.

Post-marketing requirement (PMR # 4228)
The Applicant has performed stability studies, including leachables determination, only for the samples stored in upright position, which orients the drug cartridge vertically with the crimp cap on the bottom and the plunger on the top. However, in the real-life situation, the product might be also be stored in horizontal and inverted orientations by the users. Theoretical concern remains about potential leachables when the product is stored in horizontal or inverted orientation. Also, theoretical concern remained about the lack of structural information and unusual variation observed over time in the level of the three unknown impurities during stability.

PMR # 4228
1. Perform structural identification of the specified unknown impurities observed at relative retention time (RRT) of (b) (4) (b) (4) The chemical structures of these impurities should be confirmed using physical and chemical techniques such as elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, infrared (IR) spectroscopy, X-ray crystallography, and other tests (e.g., functional group analysis, derivatization, complex formation).

2. Conduct a study in order to provide product stability and leachables data through the proposed shelf-life for three batches of to-bemarketed (TBM) drug product stored at both inverted and horizontal orientations. Manufacture these batches at the commercial site and collect stability data including leachables determination at multiple stability time-points per the testing frequency recommended in ICH Q1A(R2).

Labeling: Adequate

Manufacturing: Adequate

Lower strengths of the subject drug product (e.g., 2 mg (5 mg/mL)) are previously approved for manufacturing at the same manufacturing site (b) (4)

Manufacturing of the subject combination product is not trivial; however, many of the same sites appear to be approved in previous NDAs for the same DP but lower strengths. (b) (4) (b) (4)

(b) (4) In addition to these sites, the applicant lists five external testing sites for release and stability testing. (b) (4) (b) (4) required a PAI. The PAI is classified VAI. All other sites are recommended for approval based on inspectional history.

Biopharmaceutics: N/A

There is only one strength of the drug product in this NDA and there is no biowaiver request so no biopharm review is needed.

Microbiology (if applicable): Adequate

The method for sterilization (b) (4) (b) (4)

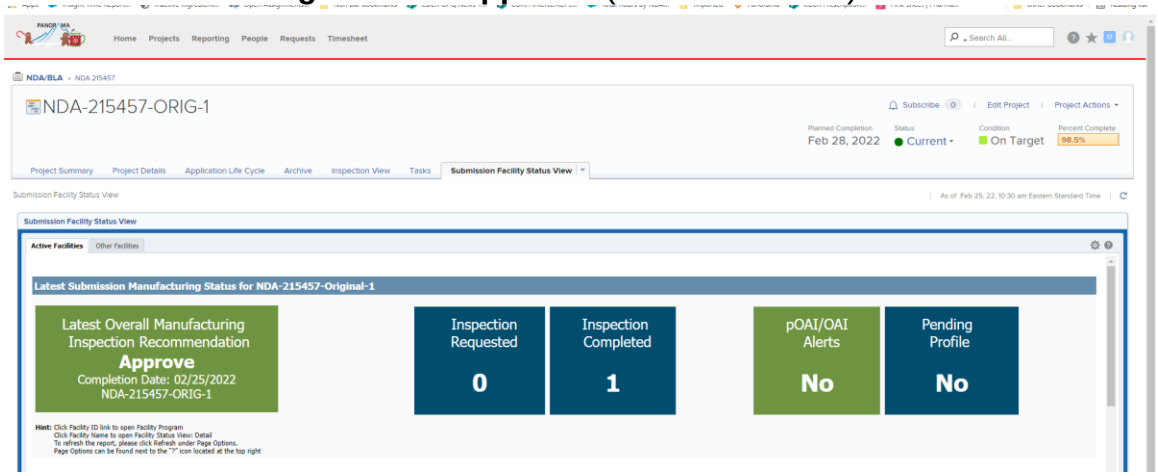
C. Risk Assessment

From Initial Risk Identification	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	
Sterility	• Formulation • Container closure • Process parameters • Scale/ equipments • Site	H		Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable (see PMR 4228)	
Uniformity of Dose (Fill Volume/ deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
pH- (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	

Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Evaluation during initial review	Acceptable (see PMR 4228)	
Appearance (Color/ turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	

Screenshot showing facilities approval (taken 25 Feb 22)



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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate; the PI complies with statutory/regulatory requirements and is consistent with guidance recommendations and CDER labeling. The revised PI label submitted by Kaleo on 02/09/2022 by email to Mun Jane has been reviewed by this reviewer.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Proposed

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	No	No proprietary name proposed
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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.	Singe-dose	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Proposed

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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)	Acceptable from CMC perspective	Also, reviewed by OND and DMEPA; see working PI label for the edits.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

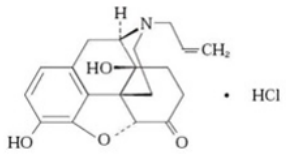
Injection: 10 mg/0.4 mL naloxone HCl solution (equivalent to 9.0 mg naloxone base) in a single-dose pre-filled auto-injector.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Strength is defined based on salt amount	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Included in description section	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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.	Singe-dose	

1.2.3 Section 11 (DESCRIPTION)

Change to:

NALOXONE HYDROCHLORIDE injection, USP, for intramuscular or subcutaneous use, is an opioid antagonist in a pre-filled, single-dose auto-injector containing 10 mg of naloxone HCL in 0.4 mL solution. NALOXONE HYDROCHLORIDE injection is not made with natural rubber latex. Chemically, naloxone HCl is the hydrochloride salt of 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:



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

Naloxone HCl 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 0.4 mL of NALOXONE HYDROCHLORIDE injection contains 10 mg of naloxone HCl (equivalent to 9.0 mg naloxone base), 3.34 mg of sodium chloride, hydrochloric acid to adjust pH, and water for injection. The pH range is 3.0 to 4.5.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	No	No proprietary name proposed
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Yes	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
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.	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	

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	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Change to (based on OND, DMEPA, CDRH and OPQ input):

16.1 How Supplied

NALOXONE HYDROCHLORIDE injection, a colorless to yellow solution of 10 mg/0.4 mL naloxone HCl, provided as follows:

NDC 60842-002-02: Package containing ten single-dose 10 mg/0.4 mL auto-injectors

16.2 Storage and Handling

Storage and Shipping

Store at controlled room temperature 15°C - 25°C (59°F - 77°F); excursions permitted between 4°C and 40°C (39°F and 104°F). Do not freeze. Protect from heat.

Use and Handling

(b) (4)

Store the NALOXONE HYDROCHLORIDE injection autoinjector in the outer case provided.

If NALOXONE HYDROCHLORIDE injection is frozen and is needed in an emergency, do NOT wait for NALOXONE HYDROCHLORIDE injection to thaw; get emergency medical help right away. Once thawed, NALOXONE HYDROCHLORIDE injection may be used.

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes; 10 auto-injectors	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	No	See change to section above
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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.	Single-dose; auto-injector	

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.)	Yes	Delete (b) (4) (b) (4) statements.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant	N/A	

has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
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.”	Included in the description section	
Include information about child-resistant packaging	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 parenterals, 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.

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	Manufactured for: Kaleo, Inc. Richmond, VA 23219	

Section 17 PATIENT COUNSELING INFORMATION: Does not include CMC drug constituent related information.

2.0 PATIENT LABELING

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

Comments are included in working PI document regarding the use of consistent storage condition (as in PI) in all patient labels.

3.0 CARTON AND CONTAINER LABELING

The most recent container closure/carton labels submitted in the email dated 02/07/2022 to Jane Mun (FDA) from Glen Kelley (Kaleo) are reviewed.

3.1 Container Label

3.2 Carton Labeling

(b) (4)

3. Outer case label

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Item	Information Provided in the NDA	Assessor's Comments about Carton/container/case Labeling
Proprietary name, established name, and dosage form (font size and prominence	No	No proprietary name proposed
Dosage strength	Yes	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes	.
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Yes	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	None	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	Yes	
No text on Ferrule and Cap overseal		
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.	Based on HCl salt amount.	
And others, if space is available		

Assessment of Carton and Container Labeling: *Adequate.*

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate.

Primary Labeling Assessor Name and Date: Renishkumar Delvadia

Secondary Assessor Name and Date (and Secondary Summary, as needed): Valerie Amspacher

Renishkumar Delvadia

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Date: 2/16/2022 08:40:55AM
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Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 2/16/2022 09:09:24AM
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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215457
Assessment Cycle Number	01
Drug Product Name/ Strength	Naloxone hydrochloride Injection / 25 mg/mL
Route of Administration	Subcutaneous or intramuscular injection
Applicant Name	Kaleo, Inc.
Therapeutic Classification/ OND Division	Opiate antagonist / N/A
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary: The submission is **recommended** for approval.

Dates of Submission(s) Covered by this Review

Submit	Received	eCTD sequence	Review Request	Assigned to Reviewer
08/31/2021	08/31/2021	#0001	N/A	09/17/2021
*10/28/2021	10/28/2021	#0004	N/A	N/A
**11/24/2021	11/24/2021	#0008	N/A	N/A
01/04/2022	01/04/2022	#0012	N/A	01/05/2022
01/21/2022	01/21/2022	#0017	N/A	01/24/2022

*New 356h identifying all facilities roles and responsibilities
**FDA Facility IR response to clarify steps for combination product assembly of autoinjector

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks:

This is an electronic submission. The Naloxone Autoinjector was developed in collaboration with the Department of Defense (DOD). Development was conducted under IND 112292 and Naloxone Auto-Injector applications from this same Kaleo applicant have been approved in NDAs 205787 (FDA approved 04/13/2014) and 209682 (FDA approved 10/19/2016). Both NDAs were reported as discontinued in the NDA Midcycle Meeting on 11/18/2021. The firm has requested Priority Review.

Goal date is 02/28/2022.

Response to the Agency's 12/15/2021 and 01/14/2022 information request letters were provided in the 01/04/2022 and 01/21/2022 submissions respectively.

Concise Description of Outstanding Issues: No outstanding issues remain.

Supporting Documents:

N205787R1.doc – Sterility assurance review of CCIT (b) (4) (b) (4) that were reviewed and found adequate in microbiology review on 03/07/2014.

DMF (b) (4) (Type V): – (b) (4) - (b) (4) Manufactured in (b) (4) (b) (4)

(b) (4) mic3.doc – Sterility assurance review of the depyrogenation of the (b) (4) stoppers that was found adequate on 11/10/2005.

D (b) (4) M33R01.doc – Sterility assurance review of the depyrogenation of the (b) (4) stoppers that was found adequate on 02/03/2017.

This review contains original information as well as response to microbiology deficiencies conveyed to the sponsor in the Agency's information request letters dated 12/15/2021 and 01/14/2022. The most recent deficiencies are italicized.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product –
(section 3.2.P.1).
Naloxone Auto-Injector (NAI) is a single-use auto-injector that delivers naloxone hydrochloride (HCl) via subcutaneous or intramuscular injection. NAI is a drug-device combination product containing a prefilled naloxone HCl drug constituent component.

The drug constituent component of NAI is a parenteral solution formulation (b) (4) glass cartridge and enclosed by an elastomeric plunger and elastomeric lined crimp cap (i.e., primary container closure).

Drug product composition –
(section 3.2.P.1).
The compositions of NAI 0.4 mg, 2 mg, and 10 mg are presented in the following table.

Component	Amount (mg/mL)		
	NAI 0.4 mg (1 mg/mL)	NAI 2 mg (5 mg/mL)	NAI 10 mg (25 mg/mL)
Naloxone HCl, anhydrous, USP, EP	1.0 mg[1]	5.0 mg[2]	25.0 mg[3]
Sodium Chloride, USP/NF, EP	8.35 mg/mL		
Hydrochloric acid, USP/NF, EP	*q.s.* to pH 3.0 – 4.5		
Water for Injection, USP/NF, EP	*q.s.* to 1 mL		
Injection Amount	0.4 mL		

1 (b) (4)
2
3

Note to Reviewer: The subject NDA provides the composition for three strengths in this section, however the 25 mg/mL (10 mg in 0.4 mL) is the composition proposed in this NDA and 356h form. No comments at this time regarding the formulations in Section 3.2.P.1 or for this NDA.

Description of container closure system –
(section 3.2.P.7).
The drug constituent component container closure system for Naloxone Auto-Injector (NAI) consists of a glass cartridge (b) (4) with a gray, (b) (4) rubber plunger on one end and an aluminum crimp cap on the other end.

Component	Description	Manufacturer
Cartridge	(b) (4) glass*	(b) (4)
Plunger	(b) (4) gray (b) (4) rubber	
Crimp cap	Silver Aluminum crimp cap	

*Cartridge dimensions listed indicate a cartridge height of (b) (4) mm and an outer diameter of (b) (4) mm.

Adequate Please see Section P.7 for assessment of the assembled autoinjector.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Valerie Amspacher

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/s/

VALERIE R AMSPACHER
02/25/2022 12:03:12 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	1/28/2022		
To:	Jane Mun		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	FDA/OC/CDER/OND/ORO/DRON/
From	Sreya Tarafdar OPEQ/OHT3/DHT3C		
Through (Division) ***Optional**	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA 215457 , Naloxone HCl Auto-injector ICC2100758 00784801		
Recommendation	**Filing Recommendation Date: 10/26/2021** ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 11/19/2021 ☐ CDRH did not provide a Mid-Cycle Recommendation ☒ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 1/25/2022 ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 215457
Sponsor	KALEO Inc.
Drug/Biologic	Naloxone HCl Auto-injector
Indications for Use	(b) (4)
Device Constituent	Auto-Injector
Related Files	ICC1901014

Review Team	
Lead Device Reviewer	*Sreya Tarafdar*

Important Dates	
Final Lead Device Review Memo Due	01/31/2022

Major Dates

Received: August 31, 2021
OPQ Kickoff Meeting: Tue 9/21/2021
OND Filing meeting: 9/23/2021
60 day Filing: 10/30/2021
74-day Letter: 11/13/2021
OPQ Midcycle Meeting: Mon 11/15/2021
OND Midcycle meeting: 11/18/2021
OPQ Wrap-up meeting: Mon 1/10/2022
OPQ Reviews Due (QDD): 1/17/2022 (new guidance is 2 weeks before ODD)
OND Wrap-up meeting: TBD
IQA due to OND (ODD): 1/31/2022
PDUFA: 2/28/2022

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:
X Approvable – the device constituent of the combination product is approvable for the proposed indication.
☐ Approvable with PMC or PMR, See Section 2.3
☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			
Human Factors Validation			X	Reviewed by DMEPA
Facilities & Quality Systems	X			Recommend inspection of (b) (4) facility for final product assembly, device performance testing. Please refer to Section 5.4. for details on the Inspection Recommendation.

2.1. Comments to the Review Team

X CDRH does not have any further comments to convey to the review team.
☐ CDRH has the following comments to convey to the review team:
Comment #:

2.2. Complete Response Deficiencies

X There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	X

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1. Scope

KALEO Inc. is requesting approval of Naloxone HCl Auto-injector. The device constituent of the combination product is a Auto-Injector.

Kaleo, Inc. is developing naloxone auto-injector (NAI) 10 mg for approval as a combination drug-device product being developed for submission under 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act).

- The Drug Constituent component of NAI is a parenteral formulation [redacted] (b) (4) glass cartridge and enclosed by an elastomeric plunger and elastomeric lined crimp cap (i.e., primary container closure).
- The Device Constituent component of NAI is a single use, pre-filled, [redacted] (b) (4), needle-based autoinjector system that delivers the prescribed dose of naloxone HCl into the user. When activated, each NAI will inject a single dose of 0.4 mL containing the appropriate amount of naloxone HCl.
- Route of administration : Intramuscular or subcutaneous injection into the thigh

CDER/OND has requested the following consult for review of the device constituent of the combination product:

We are requesting a CDRH consult for a new NDA for a device/facilities.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

• Device Performance and Reliability • Facilities

This review will not cover the following review areas:

• Human Factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

The sponsor KALEO Inc submitted a type B Pre- NDA meeting request with the application number IND 112292 in 2020, seeking the agency's feedback on the proposed studies and information to be submitted as a supplemental NDA to support the development and approval of NAI (10mg). At that time CDER requested a CDRH consult. CDRH OHT3 reviewer David Wolloscheck Provided feedback in ICC1901014. The link to the CDRH consult memo is provided below
https://force-dsc.my.salesforce.com/sfc/p/t0000000TZZf/a/t0000002J3Vt/RXNWzMVW0JpKgcMcB9WwSQaTiSsJMXP85dR6eXVOMm0

Based on the agency's feedback to Question 1 in 2020 IND 112292 type B Pre- NDA meeting request, the sponsor has now submitted a new NDA for the approval of NAI (10mg).

3.3. Indications for Use

Combination Product	Indications for Use
Naloxone HCl Auto-injector	[redacted] (b) (4)
Auto-Injector	Delivery of the Drug Product

The sponsor states the Proposed indication statement as follows :- (from module 2.3 Introduction to quality overall summary >> proposed indication)

(b) (4)

3.4. Materials Reviewed

Materials Reviewed		
Sequence	**Module(s)**	
\\CDSESUB1\evsprod\NDA215457\0001	2.2	CTD introduction
	2.3.D	Quality Overall Summary Finished Product
	3.2.P.7	Container Closure System
	3.2.A	Facilities and Equipment
	1.14	Labeling

4. DEVICE DESCRIPTION

4.1. Device Description

The Device Constituent Component of NAI is a compact, user-actuated, (b) (4) single use autoinjection system that delivers naloxone HCl through a needle into the patient once activated. The needle is fully retracted within the device housing following use. Identification of the external components of the Device Constituent Component of NAI 10 mg is in Figure 3.2.D.1.1-1.

(b) (4)

Figure 3.2.D.1.1-1: NAI 10 mg External Component Description

When activated, each NAI will inject a single dose of 0.4 mL containing the appropriate amount of naloxone HCl. NAI is designed to be a single use device, so any residual parenteral formulation remaining in the device after injection of the dose cannot be utilized. NAI is filled to a nominal volume of (b) (4) mL, so approximately (b) (4) mL residual drug product remains in NAI after activation.
The container closure system consists of a (b) (4) glass cartridge, a (b) (4) gray (b) (4) rubber plunger, and an aluminum-crimping cap (no product contact) with a (b) (4) gray (b) (4) rubber seal (which has product contact). The product-contact materials used comply with the USP and European Pharmacopoeia (EP) and are considered suitable for the storage of sterile bulk drug product solution.
The Device Constituent Component of Naloxone Auto-Injector (NAI) is a self-contained auto-injection device that requires no assembly, priming or attachments. The outer case is made (b) (4) and is designed to protect NAI during normal use. In addition, the naloxone solution can be seen through a drug viewing window located on the outer case to inspect the drug prior to use. NAI is activated by first removing the outer case. The user then pulls a red safety guard that is located on the same end as the needle and presses the black base against the injection site (i.e., patient's thigh). Removing the red safety guard also removes the needle sheath protecting the needle. The black base cannot be depressed without removing the red safety guard. This design feature helps prevent premature activation of NAI.

(b) (4)

Materials of construction and manufacture are shown in Figure 3.2.D.2.4-1 and are listed by corresponding number along with the material description in Table 3.2.D.2.4-1.
Components with materials that come into contact with the drug solution (i.e., drug solution fluid path) are also indicated in the Table 3.2.D.2.4-1. The engineering specification drawings for each component are listed in Table 3.2.D.2.4-2. For more information regarding biocompatibility, refer to Section 3.2.D.2.6.

4.2. Steps for Using the Device

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments The Sponsor provided a detailed and full description of the device with engineering drawings, dimensions and steps for use of the device. No further deficiencies were identified.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: X Yes ☐ No		

	Date Sent: 11/23/2021	Date/Sequence Received: 11/27/2021
Information Request #	(b) (4)	
Sponsor Response		
Reviewer Comments	The sponsor has clarified the steps involved in the final finished combination product assembly and also provided fair description of which facilities are responsible for each of the steps.	
Response Adequate:	X **Yes** ☐ **No** Click or tap to enter a date.	

Add Additional Information Request

5. FILING REVIEW

CDRH performed Filing Review	X
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist	
Description	**Present**

		Yes	No	N/A
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability	X		
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment
The filing review checklist is complete. sponsor has provided all items listed in the above filing review checklist.

5.2. Facilities Information

(b) (4)

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(b) (4)

5.3. Quality System Documentation Triage Checklist

Device Type Table

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☒ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☒ No ☐ UNK
Is the final combination product meant for emergency use?	☒ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)? Target population includes military & civilian first responders, adult and children 12 years and older (*with known or suspected opioid exposure prior to or after the onset of respiratory and/or central nervous system depression*)	☒ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☒ No ☐ UNK

Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	X Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes X No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION

Acceptable for Filing: X Yes ☐ No (Convert to a RTF Memo) ☐ N/A

Facilities Inspection Recommendation:
X (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance
☐ No Inspection ☐ N/A

Site(s) needing inspection:

Firm Name: (b) (4)
FEI: (b) (4)

Reviewer Comments

The submission is acceptable for filing.
Inspection Recommendation:

(b) (4)

(b) (4)

Refuse to File Deficiencies: ☐ Yes X No ☐ N/A

74-Day Letter Deficiencies: ☐ Yes X No ☐ N/A

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Symbols on device constituent and packaging	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X (DMEPA review)		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

The labeling is acceptable. The IFU and instructions for Use are acceptable and are consistent in all labeling.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The labeling is acceptable. The IFU and instructions for Use are acceptable and are consistent in all labeling.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health			
Version history demonstrates risk management throughout design / development activities			
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments The overall design control process is acceptable.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)

Reviewer Comments
Please refer to Section 9.1.1 for a detailed table of all tested and validated design inputs/outputs.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 10993-1:2018 *Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process*	Y	Y
ANSI/AAMI/ISO (b) (4)	Y	Y
ISO 11608-1:2015 *Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems*	Y	Y
Guidance for Industry: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (June 2013)	Y	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No		

8. RISK ANALYSIS

8.1. Risk Management Plan

The risk management plan is divided into a User-FMEA, Design-FMEA, Process-FMEA, and a Fault Tree Analysis (FTA), URRA, and PCA Task analysis. Since this device is intended to be used by a lay user in an emergency situation, the Sponsor should demonstrate that the device is sufficiently reliable to ensure that the device is able to successfully deliver the intended dose.

Section 3.2.D.2.3. summarizes the risk Management plan, risk and hazard analysis for NAI 10mg. the following documents details each of the risk analyses:

PCA Task Analysis (KA-201DI-002)
UFMEA (KA-201DI-002)
UFMEA after completion of the human factors validation studies (KA-1000SE-002 and KA-1001SE-002)
URRA (KA-203DI-002)
DFMEA (KA-401RM-002)
PFMEA (PFMEA-401-004 and PFMEA-401-002)
NAI 10 mg Reliability Summary Report (RPT-DVL-0049)

The NAI 10 mg mechanical drug delivery system is the same as NAI 2 mg. Fulfillment letters were received for the two NAI 2 mg post-marketing requirements (PMR 3135-1 and PMR 3135-2). PMR-3135-1 was to establish reliability requirements for the combination product and to complete testing that verified combination product reliability. The fulfillment letter was received on May 8, 2019. PMR 3135-2 was to conduct a case study analysis of reports of failure of the combination product to activate, or failure of the product to deliver the full-labeled dose. The fulfillment letter was received on July 5, 2019.
In the pre-NDA meeting held on February 24, 2020, (refer to Question 17 Meeting Minutes – Type B – 24 Feb 2020) it was determined that NAI 10 mg could leverage some of all of the reliability data for NAI 2 mg. Differences between the devices would require supporting information that the device reliability is not impacted.

Based on the review of the NAI 2 mg device reliability reports, risk and fault tree analyses, and *in vitro* performance data generated for NAI 10 mg, the device reliability of NAI 10 mg at release and through shelf-life is comparable to the device reliability of NAI 2 mg. Naloxone Auto-Injector 10 mg is comparable to NAI 2 mg for the system level "Failure-to-Fire" attribute previously and worst-case device reliability data through shelf-life. Furthermore, the system level reliability for "Failure to Fire", established through quantitative fault tree analysis, determined the probable failure rate, associated with the NAI 2 mg or NAI 10 mg system level to be (b) (4) failures per million devices, which complies with the *Draft Guidance for Industry and Food and Drug Administration Staff: Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA* (April 2020), which recommends a successful injection reliability of 99.999% with a 95% level of confidence. Therefore, there is no impact to the device design or device manufacturing process from NAI 2 mg to NAI 10 mg.

An evaluation was conducted to compare NAI 10 mg with NAI 2 mg with regards to the possibility of a failure to fire. The device components of both NAI 10 mg and NAI 2 mg are identical.
The fault tree analysis (FTA) contained in the original reliability report for NAI 2 mg (RPT-DEV-0009) was evaluated with respect to the changes made for NAI 10 mg. The existing FTA applies equally to NAI 10 mg as it does NAI 2 mg.

Table 3.2.D.2.3.1.6-1 – PQ Data Analysis for NAI 10 mg

Characteristic	Lot #	Ppk*	Mean	SD	Min	Max
						(b) (4)

AF	(b) (4)
VD	
DT	
ENL	

*: (b) (4)

Abbreviations: AF: Activation Force; DT: Dispensing Time; ENL: Exposed Needle Length; Min: Minimum value; Max: Maximum value; SD: Standard deviation; VD: Volume Dispensed

Table 3.2.D.2.3.1.6-2 – Accelerated Aging Data Analysis for NAI 10 mg

Characteristic	Shelf-Life Specification	Storage Time (Days) at 60°C (accelerated aging conditions)						
		0	14	28	42	56	70	84
		(b) (4) Sample ID:						(b) (4)
Volume Dispensed (mL)	(b) (4)	Mean						
		SD						
		Min						
		Max						
		Ppk *						
Exposed Needle Length (in)		Mean						
		SD						
		Min						
		Max						
		Ppk *						
Activation Force (lbs)		Mean						
		SD						
		Min						
		Max						
		Ppk *						
Dispensing Time (sec)		Mean						
		SD						
		Min						
		Max						
		Ppk *						

*: (b) (4)

Reviewer Comments
The risk assessment and reliability was reviewed and is acceptable. The Sponsor identified a detailed reasonable design requirements for each aspect of risk analysis, provided in the respective documents. The conducted reliability performance testing was reviewed and found adequate (see above). Hence, the risk analysis and demonstration of device reliability is acceptable.

8.2. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments Please see review conclusions above. The risk analysis was found to be acceptable.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

(b) (4)

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4.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☒ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 1/14/2022	**Date/Sequence Received: Seq 0017** 1/21/2022
Information Request #	(b) (4)	
Sponsor Response		
Reviewer Comments		

	(b) (4) However, the acceptance criteria and spec limits are acceptable and that both the devices' forces were within the acceptable range of spec limits – is acceptable. (b) (4)
Response Adequate:	☐ **Yes** X **No, See IR # Sent on 1/25/2022**

	Date Sent: 1/25/2022	**Date/Sequence Received: Seq 0017 1/26/2022**
Information Request #	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	The sponsor has attributed (b) (4) However since all the AF data was within the release specifications it is acceptable.
Response Adequate:	X **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

4.3. Discipline Specific Sub-Consulted Review Summary

X No Additional Discipline Specific Sub-Consults were requested

☐ The following additional Discipline Specific Sub-Consults were requested:

5. CLINICAL VALIDATION REVIEW

5.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review

X There are clinical studies for review

This information was obtained from the following **documents**: 2.7 Clinical Summary

Table 2.7.6-1 Listing of Clinical Studies

Type of Study	Study Identifier	Locationof Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dose Regiment, Route of Administration	Number of Subjects	Heathy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status / Type of report
Safety / Bio-availability (BA) / Bio-equivalence	IJ-900DV-03O	NDA 205787 5.3.1.2	Primary: To compare the pharmacokinetics (PK) of 0.4 mg naloxone hydrochloride (HCl) following a single intramuscular (IM)/ subcutaneous (SC) injection administered using either a naloxone auto-injector (NAI) or a standard syringe. Secondary: To assess the safety and tolerability of naloxone HCl injection by NAI compared to standard syringe.	Randomized, single dose, single blind, twosequence, two period crossover bioavailability, safety, and tolerability study in fasted, healthy male and female subjects.	Test: A single IM/ SC injection of 0.4 mg naloxone HCl administered using NAI. Reference: A single IM/ SC injection of 0.4 mg naloxone HCl administered using a standard syringe.	30	Healthy	3 days for in-patient admission to complete two dosing periods	Complete/ Full

Type of Study	Study Identifier	Locationof Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dose Regiment, Route of Administration	Number of Subjects	Heathy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status / Type of report
Safety / BA / Dose proportion-ality	KA-900DV-05A	NDA 209862 5.3.1.2	Primary: To evaluate the dose proportionality of 0.4 mg and 2 mg naloxone HCl following IM/SC injection using NAI and to characterize the PK profiles of 0.4 mg, 0.8 mg (two NAI 0.4 mginjections), and 2 mg naloxone HCl following IM/SC injection using NAIs. Secondary: To assess the safety and tolerability of 0.4 mg, 0.8 mg, and 2 mg naloxone HCl injection using NAIs.	Randomized, single dose, six-sequence, three period crossover bioavailability, dose proportionality, safety and tolerability study in fasted, healthy, male and female subjects.	Test 1: a single IM/ SC injection of 2 mg naloxone HCl administered using NAI Test 2: Two IM/ SC injections of 0.4 mg naloxone HCl administered two minutes apart using NAIs (0.8 mg naloxone HCl dose) Reference: a single IM/ SC injection of 0.4 mg naloxone HCl administered using NAI	24	Healthy	4 days for in-patient admission to complete three dosing periods	Complete/ Full

Type of Study	Study Identifier	Locationof Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dose Regiment, Route of Administration	Number of Subjects	Heathy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status / Type of report
Safety / BA / Dose proportionality	KA-900DV-002	5.3.1.2 (full study report) Synopsis	Primary: To evaluate the dose proportionality of 2 mg and 10 mg naloxone HCl following IM/SC injection using NAI and to characterize the PK profiles of 2 mg and 10 mg naloxone HC following IM/SC injection using NAIs. Secondary: To assess the safety and tolerability of 2 mg and 10 mg naloxone HCl injection using NAIs.	Randomized, single dose, single blind, two-sequence, two period crossover bioavailability, safety, and tolerability study in fasted, heathy male and female subjects.	Test: A single IM/SC injection of 10 mg naloxone HCl administered using a NAI Reference: A single IM/SC injection of 2 mg naloxone HCl administered using a NAI	24	Healthy	6 days for in-patient admission to complete two dosing periods	Complete/ Full

Study Name	A Randomized, Two-Sequence, Two-Period, Pharmacokinetic Bioavailability and Dose Proportionality Study of Naloxone Hydrochloride 10 mg Administered Using a Naloxone Auto-Injector in Healthy Human Volunteers
Study Type	Phase 1, pharmacokinetic bioavailability, and dose proportionality
Objectives/Endpoints	The primary objectives of the study were: • To evaluate the dose proportionality of 2 mg and 10 mg naloxone hydrochloride (HCl) following intramuscular (IM)/subcutaneous (SC) injection using a naloxone auto-injector (NAI). • To characterize the pharmacokinetic (PK) profiles of 2 mg and 10 mg naloxone HCl following IM/SC injection using an NAI. The secondary objective of this study was to assess the safety and tolerability of 2 mg and 10 mg naloxone HCl injection using an NAI.

Drug/Device Studied

IMP	Name	Strength	Route	Lot No.	Manufacturer
Reference	Naloxone HCl Injection 2 mg Auto-Injector, the authorized generic for EVZIO (NAI 2 mg)	5 mg/mL naloxone HCl	IM or SC	F0124619DD	(b) (4)
Test	Naloxone Auto-Injector 10 mg (NAI 10 mg)	25 mg/mL naloxone HCl	IM or SC	F0121820JJ	Sponsor (kaleo, Inc.)

HCl = hydrochloride; IM = intramuscular; IMP = investigational medicinal product; SC = subcutaneous

Number and Type of Subjects

Study Subjects:	
Planned for Inclusion:	24 subjects
Enrolled and Randomized:	24 subjects
Excluded:	No subjects were excluded from the analyses.
Analyzed:	24 subjects in the Safety Population and 24 subjects in the Pharmacokinetic Population.
Diagnosis and Inclusion Criteria:	
Healthy adult male and female subjects, 18 to 55 years of age (inclusive) with a body mass index between 18.5 and 32.0 kg/m^2 and a weight of $\geq$ 50.0 kg and $\leq$ 100.0 kg were enrolled in this study. Women of childbearing potential could be enrolled.	

Brief description of protocol

Study Design:
This was a randomized, open-label, single-dose, 2-sequence, 2-period crossover study in fasted, healthy, male and female volunteers to evaluate the dose proportionality of 2 mg and 10 mg naloxone administered using an NAI. The PK profiles of these 2 NAI dosage strengths were characterized.

Methodology:
Subjects were randomly assigned to receive 1 of 2 treatment sequences (AB, BA) with treatments defined as follows:

- Treatment A: IM/SC administration of 2 mg naloxone HCl with a single injection using an NAI (Reference).
- Treatment B: IM/SC administration of 10 mg naloxone HCl with a single injection using an NAI (Test).

At the Screening Visit (between Day –28 to Day –3), subjects signed the informed consent forms (ICFs) for the study and for testing and monitoring procedures for coronavirus disease 2019 (COVID-19) and then completed procedures to determine eligibility. Subjects determined to be eligible after completion of screening procedures reported to the Early Phase Clinical Unit (EPCU) on Day -2 where their eligibility and COVID-19 status were reassessed. Eligible subjects were randomly assigned to a treatment sequence and on Day 1, subjects received the first dose of investigational medicinal product (IMP) followed by 12 hours of PK sampling. There was a washout period of at least 47 hours between doses and subjects remained at the EPCU during the washout period. On Day 3, subjects completed the second dose administration followed by 12 hours of PK sampling.
Safety assessments including physical examination, electrocardiogram (ECG), vital signs, cardiac telemetry monitoring, clinical laboratory tests, injection site assessments, adverse events (AEs), and concomitant medication were conducted and recorded throughout the study. Subjects were discharged from the EPCU on Day 4.

Duration of Treatment:
The duration of study participation for each subject was less than 5 weeks (screening period from Day -28 to Day -3 and in-house admission from Day -2 to Day 4 to complete the 2 dosing periods [i.e., Treatment A and Treatment B]).

Treatment Compliance:
Dosing was performed by trained EPCU personnel designated by the Investigator. The date and time of dosing was documented on each dosing day. Comments were recorded if there were any deviations from the planned dosing procedures. Subjects who were significantly noncompliant

	could have been discontinued. All study procedures were performed by qualified study personnel who were trained on the protocol. Compliance was also verified by Sponsor audit of the source documents.
Results	**Pharmacokinetic Results:** Mean dose-normalized naloxone plasma concentrations were similar for NAI 2 mg and NAI 10 mg in the elimination phase after about 2 hours following IM/SC dosing, but were higher in general with NAI 10 mg in the absorption/distribution phase from dosing to about 2 hours post dose. Naloxone was rapidly absorbed following IM/SC administration of NAI 2 mg and NAI 10 mg to healthy subjects. The median T_{max} (range) was 0.17 hour (0.08 to 0.67 hours) and 0.26 hour (0.09 to 0.67 hours) for NAI 2 mg and NAI 10 mg, respectively. Naloxone was cleared from plasma rapidly with a mean half-life of approximately 1.5 hours for both doses. The geometric mean C_{max} (geometric %CV) was 6.24 ng/mL (52.1%) and 37.8 ng/mL (48.5%) for NAI 2 mg and NAI 10 mg, respectively. The geometric mean (geometric %CV) for systemic naloxone exposure (AUC_{0-t}) was 9.12 h*ng/mL (15.1%) and 50.3 h*ng/mL (17.8%) for NAI 2 mg and NAI 10 mg, respectively. The AUC_{0-inf} was almost identical to the AUC_{0-t} for both doses. Naloxone exposure during the early absorption phase was greater for NAI 10 mg compared to NAI 2 mg. Geometric mean partial AUCs were 0.00875 and 0.0295 h*ng/mL ($AUC_{0-2.5min}$), 0.0721 and 0.288 h*ng/mL (AUC_{0-5min}), 0.392 and 1.81 h*ng/mL ($AUC_{0-10min}$), and 0.809 and 4.20 h*ng/mL ($AUC_{0-15min}$) for NAI 2 mg and NAI 10 mg, respectively. Based on an ANOVA, naloxone exposure was dose proportional for the comparison of NAI 10 mg and NAI 2 mg for AUC_{0-t} and AUC_{0-inf} with dose-normalized geometric mean ratio (90% CI) of 1.10 (1.06, 1.15). Dose-normalized C_{max} was slightly greater than dose proportional (1.21 [1.07,1.37]). Based on the power model, naloxone exposure was linear and dose proportional for the comparison of NAI 10 mg and NAI 2 mg as evident by the estimated values of the slope being close to 1.00 for C_{max}, AUC_{0-t}, and AUC_{0-inf} (slope [90% CI] 1.12 [0.95, 1.29], 1.06 [1.00, 1.12], 1.06 [1.00, 1.12], respectively). **Safety Results:** There were no serious AEs (SAEs), deaths or treatment-emergent AEs (TEAEs) that led to discontinuation from the study. Overall, 5 subjects (20.8%) experienced 7 TEAEs after receiving NAI 10 mg. No TEAEs were reported after administration of NAI 2 mg. Reported TEAEs included feeling hot (in 3 subjects [12.5%]), injection site pain, headache, and rash erythematous (in 1 subject each [4.2%]). All TEAEs were considered mild by the Investigator and were considered probably related or related to the IMP except for 1 TEAE of headache (considered unlikely to be related). For the preferred term of injection site pain, 1 subject experienced 2 mild injection site reactions (pain and tenderness) that did not require treatment and resolved within 3 hours. All TEAEs had an outcome of recovered/resolved. There were no clinically significant safety laboratory values, vital signs, ECG values, cardiac telemetry assessments, or physical examinations findings. **Discussion and Conclusion:** This was a randomized, open-label, single-dose, 2-sequence, 2 period crossover study in fasted, healthy male and female subjects to evaluate the dose proportionality of 2 mg and 10 mg naloxone administered using an NAI. Twenty-four subjects were randomized to receive the study treatments (Treatment A: NAI 2 mg, Treatment B: NAI 10 mg) in 1 of 2 sequences (AB or BA). All 24 subjects completed the study per protocol. **Safety Discussion and Conclusions** No safety concerns were noted in the safety laboratory values, vital signs, ECG values, cardiac telemetry assessments, injection site evaluations or physical examinations findings during the study. Overall, 5 subjects (20.8%) experienced 7 TEAEs (all after receiving NAI 10 mg). The most frequently reported TEAE was feeling hot (reported in 3 subjects). All TEAEs were considered mild in intensity by the Investigator. All TEAEs were considered probably related or related to study treatment except 1 TEAE of headache that was considered unlikely to be related. One subject experienced mild injection site reactions (pain and tenderness). All TEAEs had an outcome of recovered/resolved. There were no deaths, SAEs or discontinuations associated with study treatment. **Conclusion** Naloxone exposure after IM/SC administration of NAI 2 mg and NAI 10 mg in healthy subjects was linear and dose proportional, with dose-normalized C_{max} slightly greater than dose proportional. Naloxone was rapidly absorbed following administration of NAI 2 mg and NAI 10 mg with the 10 mg dose resulting in higher exposure in the early absorption phase through the entire 12-hour sampling period. Maximum plasma naloxone concentration occurred at 0.17 to 0.26 hours and naloxone was cleared from plasma rapidly with a mean half-life of approximately 1.5 hours for both doses. Both NAI 2 mg and NAI 10 mg were safe and well tolerated when administered to healthy subjects in this study.
Device Related Comments	No device specific comments were found in the protocol.
Reviewer Comments	• There were no serious AEs (SAEs), deaths or treatment-emergent AEs (TEAEs).

	• Overall, 5 subjects (20.8%) experienced 7 TEAEs after receiving NAI 10 mg. No TEAEs were reported after administration of NAI 2 mg. 3 subjects [12.5%] reported feeling hot ; 1 subject each [4.2%] reported injection site pain, headache, and rash erythematous. • All TEAEs were considered mild by the Investigator and were considered probably related to the IMP except for 1 TEAE of headache (considered unlikely to be related). For the preferred term of injection site pain, 1 subject experienced 2 mild injection site reactions (pain and tenderness) that did not require treatment and resolved within 3 hours. All TEAEs had an outcome of recovered/resolved. There were no clinically significant safety laboratory values, vital signs, ECG values, cardiac telemetry assessments, or physical examinations findings. No severe AE was related to the device. No other safety events were reported that could be related to the device.
Reviewer Conclusion	No adverse events were reported that would indicate an issue with the device.

5.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☒ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☒ No ☐ N/A
Reviewer Comments A total of three studies were conducted. The first study evaluated NAI 0.4 mg, the second study evaluated the NAI 2mg and the third study evaluated the NAI 10mg. Based on the current study outlined/cited above, there were no specific adverse events that could be directly linked to the syringe or auto-injector. The Sponsor stated that the to-be-marketed auto-injector NAI 10mg was used in the study.		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

6. HUMAN FACTORS VALIDATION REVIEW

** **NOTE** : Human Factors Validation was not reviewed by CDRH since DMEPA is reviewing this.

7. FACILITIES & QUALITY SYSTEMS

7.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	
CDRH Facilities Inspection Review was not conducted	X

7.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	X
CDRH Quality Systems Documentation Review was not conducted	

7.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

(b) (4)

The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

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Table 3.2.D.3.1.3-1: Summary of Applicable Device Quality System Information for NAI Included in this New Drug Application

QS Activity	(b) (4)	kaleo, Inc.
Design Controls		
Design Controls, General, 820.30(a)		X
Design and Development Planning, 820.30(b)		X
Design Input, 820.30(c)		X
Design Output, 820.30(d)		X
Design Review, 820.30(e)		X
Design Verification, 820.30(f)		X
Design Validation, 820.30(g)		X
Design Transfer, 820.30(h)		X
Design Changes, 820.30(i)		X
Design History File, 820.30(j)		X
Manufacturing Information		
Quality System Procedures, 820.20(e)	X	X
Purchasing Controls, 820.50	X	X
Production and Process Controls, 820.70	X	
Inspection, Measuring, and Test Equipment, 820.72	X	
Process Validation, 820.75	X	X
Process Validation, 820.75(a)	X	
Receiving Acceptance Activities, 820.80(b)	X	
Final Acceptance Activities, 820.80(d)	X	X
Nonconforming Products, 820.90	X	X
Corrective and Preventive Action (CAPA), 820.100	X	X
Complaint Files, 820.198	X	X
Servicing, 820.200	N/A to NAI	

Reviewer comments
The sponsor has provided adequate information for the manufacturing process , production flow off the device constituent of the combination product including (b) (4) (b) (4) The sponsor has also provided the key quality systems for the involved facilities as a summary in the table provided above. All the information provided by the sponsor is acceptable.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

7.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:

☐ Device QSR-based

X Drug cGMP-Based Streamline – Review Instructions

☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): • (b) (4) • Kaleo • (b) (4)	**Reviewer Discussion** – The following are kaleo, Inc.'s basic internal quality systems procedures: •SOP-QMS-0011 – Responsibilities of Quality Assurance •SOP-QA-0002 – Internal Audits •SOP-QMS-0007 – Management Review Quality Systems are controlled under the following (b) (4) documents(s): • (b) (4) Quality Manual • (b) (4) Batch Record Control • (b) (4) Quality System Record Control • (b) (4) Employee Training • (b) (4) Change Management The procedure for Quality Systems (b) (4) Quality Manual. Refer to Section 3.2.D.3.3 for all applicable (b) (4) Quality System Documents.
21 CFR 820.30 Summary of Design Controls	Firm(s): Kaleo	**Reviewer Discussion** – Reviewed in detail in Section 7
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): • (b) (4) • Kaleo • (b) (4)	**Reviewer Discussion** – The following are kaleo, Inc.'s procedures for purchasing controls: •SOP-OPS-0005 – Supplier Audits •SOP-OPS-0008 – Supplier Qualification •SOP-OPS-0009 – Change Control •SOP-MFG-0001 – Purchasing Controls Sponsor provided procedures for controlling purchasing of components (b) (4) for use in the manufacture of NAI in 32d33-qsi-toc.pdf on pages 70-79 of 1805. Purchase Controls are controlled under the following (b) (4) documents(s): • (b) (4) Product Acceptance and Release • (b) (4) Purchasing Sponsor provided procedures for controlling purchasing of components (b) (4) for use in the manufacture of NAI in 32d33-qsi-toc.pdf on pages 498-504 of 1805.

		Purchase Controls are controlled under the following (b) (4) documents(s): • (b) (4) Purchasing Controls Sponsor provided procedures for controlling purchasing of components (b) (4) for use in the manufacture of NAI in 32d33-qsi-toc.pdf on pages 1181-1188 of 1805.
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s):	**Reviewer Discussion** – Reviewed in Section 12.2.3.
21 CFR 820.170 Summary of Installation	Firm(s):	**Reviewer Discussion** – **N/A**
21 CFR 820.200 Summary Servicing	Firm(s):	**Reviewer Discussion** – **N/A**
Subpart F – Identification and Traceability	Firm(s):	**Reviewer Discussion** – **N/A**
Subpart G – Production and Process Controls	Firm(s):	**Reviewer Discussion** – Reviewed in Section 12.3
Subpart H – Acceptance Activities § 820.80 - Receiving, in-process, and finished device acceptance.	Firm(s): • (b) (4) • Kaleo • (b) (4)	**Reviewer Discussion** – The following are kaleo, Inc.'s procedures for purchasing controls: final acceptance activities • SOP-QMS-0017 – Review and Disposition of Batches. The procedure for Receiving Activities (b) (4) (b) (4) Product Identification and Traceability Final Acceptance Activities are controlled under the following (b) (4) documents(s): • (b) (4) In Process and Final Inspections Receiving and final acceptance Activities are controlled under the following (b) (4) documents(s): • (b) (4) Product Acceptance and Release
Subpart I – Nonconforming Product § 820.90	Firm(s):	**Reviewer Discussion** – The following procedures are used for handling non-conforming NAI product at kaleo, Inc.: •SOP-OPS-0004 – Deviation Management •SOP-QMS-0022 – Issues Management Nonconforming Product is controlled under the following (b) (4) documents(s): • (b) (4) Control of Nonconforming Product

		Nonconforming Product is controlled under the following (b) (4) documents(s): • (b) (4) Nonconformances
Subpart K – Labeling and Packaging Controls	Firm(s):	**Reviewer Discussion – N/A**
Subpart L – Handling, Storage, Distribution	Firm(s):	**Reviewer Discussion – N/A**
Subpart M – Records § 820.198 - Complaint files.	Firm(s):	**Reviewer Discussion –** The following are the procedures for handling complaints at kaleo, Inc.: • SOP-OPS-0007 – Field Alert Reporting, Market Withdrawals, and Product Recalls • SOP-QMS-0016 – Complaint Processing • WI-QMS-0016 – Managing Complaint Records in MasterControl NAI is a drug/device combination product with the primary mode of action being the drug. Therefore, NAI adverse experiences are reported in compliance with 21 CFR 314.80. Complaints are controlled under the following (b) (4) documents(s): • (b) (4) Customer Complaints Complaints are controlled under the following (b) (4) documents(s): • (b) (4) Complaint Processing
Subpart O – Statistical Techniques	Firm(s):	**Reviewer Discussion – N/A**

Reviewer Comments
Kaleo, (b) (4) have indicated compliance with the relevant callouts (820.20, .30, .50, .80, .90, .198 and .100). See below for a review of the CAPA system.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	X Yes	☐ No

7.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

CAPA is controlled under the following [(b) (4)] documents(s):
• [(b) (4)] Corrective and Preventive Action

The following procedures are for the corrective and preventive action system at kaleo, Inc.:
• SOP-QMS-0014 – CAPA Management

CAPA is controlled under the following [(b) (4)] documents(s):
• [(b) (4)] Corrective and Preventive Action

Kaleo is responsible for oversight of CAPA [(b) (4)] that relates to the NAI Cartridge Assembly System as well as the manufacture, testing, and control of the NAI Cartridge Assembly product.

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	Present
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	Yes
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	Yes
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	Yes
Investigations into the cause of nonconformities relating to product, processes, and the quality system	Yes
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	Yes
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	Yes
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	Yes
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	Yes
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	Yes
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	Yes
Requires documentation of all CAPA activities	Yes
CAPA Conclusion	
The Sponsor provided adequate information for corrective and preventive actions.	☒Yes ☐No

7.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

(b) (4)

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Reviewer Comments
Overall, this control strategy appears appropriate to ensure that the devices meet their EPRs at release.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

7.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes X No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes X No ☐ N/A	**Final Deficiencies:** ☐ Yes X No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes X No		

<<END OF REVIEW>>

8. APPENDIX A (INFORMATION REQUESTS)

8.1. Filing/74-Day Information Requests

8.2. Mid-Cycle Information Requests

8.3. Interactive Information Requests

8.3.1. Interactive Information Requests sent on 11/23/2021

(b) (4)

8.3.2. Interactive Information Requests sent on 1/14/2022

(b) (4)

8.3.3. Interactive Information Requests sent on 1/25/2022

(b) (4)

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/s/

JANE J MUN
03/02/2022 12:41:39 PM