

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205787Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

07 MAR 2014

NDA: 205-787

Drug Product Name

Proprietary: Evzio (proposed)

Non-proprietary: Naloxone hydrochloride injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
13 SEP 2013	13 SEP 2013	13 SEP 2013	13 SEP 2013
27 SEP 2013	27 SEP 2013	N/A	N/A
09 OCT 2013	10 OCT 2013	N/A	N/A
20 DEC 2013	20 DEC 2013	N/A	N/A
20 JAN 2014	22 JAN 2014	N/A	N/A
11 FEB 2014	11 FEB 2014	N/A	N/A
03 MAR 2014	04 MAR 2014	N/A	N/A

Applicant/Sponsor

Name: Kaleo
Address: 111 Virginia Street Suite 405
Richmond, VA 23219
Representative: Ronald D. Gunn
Telephone: 804-545-6376

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

- A.**
1. **TYPE OF SUBMISSION:** New 505(b)(2) NDA
 2. **SUBMISSION PROVIDES FOR:** A new combination drug/device product
 3. **MANUFACTURING SITE:** (b) (4)
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Single use autoinjector with voice prompts
 - 0.4 mg/0.4 mL sterile, (b) (4) naloxone in a glass cartridge
 - Intramuscular or subcutaneous injection
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Treatment of opioid-induced respiratory depression
- B.** **SUPPORTING/RELATED DOCUMENTS:** Microbiology review of IND 112,292 dated 04 June 2013. Microbiology review of NDA 201-739 dated 13 May 2011. Microbiology review of DMF (b) (4) dated 20 August 2013.
- C.** **REMARKS:** This NDA is in the eCTD format and is a rolling submission that was granted an expedited review process. The reference product is described in NDA 16-636. The CMC information is in the 4th submission, dated 13 September 2013. The device information was provided in the 20 December 2013 submission. During the rolling review process the NDA holder changed from Intelliject, Inc. to Kaleo, Inc.

The following information request was sent to the sponsor on 26 September 2013 and a response was received on 10 October 2013.

1. Provide a description of and a summary of the results from the sterility and endotoxin method verification studies for the drug product constituent (Naloxone hydrochloride).
2. Provide a description of and a summary of the results from (b) (4) validation studies for the drug constituent manufacturing process. Include:
 - a. (b) (4)
 - b. (b) (4)
 - c. (b) (4)

3. Provide a description of the media and incubation conditions for the environmental monitoring program.
4. Define x in table 3.2.P.3.5.3-12.
5. Indicate the number of filling lines in Clean Room (b) (4).
6. Provide a description of the (b) (4) and the initial qualification run dates.
7. Provide the following information for the (b) (4) used to support Naloxone manufacture:
 - a. The number of units filled
 - b. The number of units rejected, with a brief explanation of the reason for the rejection
 - c. The number of units incubated
 - d. The number of positive units
 - e. The line speed
 - f. The container closure system used
 - g. A summary of growth promotion studies

The following information request was included in the 74-day letter sent on 22 January 2014 and a response was received on 11 February 2014.

(b) (4)



Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended for approval
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This is a combination drug/device product. The drug is (b) (4) and filled into a glass cartridge. The filled glass cartridge is assembled with the needle and protective sheath. This cartridge assembly is sterilized (b) (4)
- B. Brief Description of Microbiology Deficiencies** – Not applicable
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable
- D. Contains Potential Precedent Decision(s)** - Yes No

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, PhD
- B. Endorsement Block** _____
Bryan Riley, PhD
Microbiology Team Leader
- C. CC Block**
In DARRTS

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

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

/s/

JESSICA COLE
03/07/2014

BRYAN S RILEY
03/07/2014
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 205-787

Applicant: Kaleo, Inc.
(formerly Intelliject)

Letter Date: 20 December 2013

Drug Name: 0.4 mg Naloxone Auto-injector (Naloxone hydrochloride, USP)

NDA Type: 505(b)(2)

Stamp Date: 20 December 2013

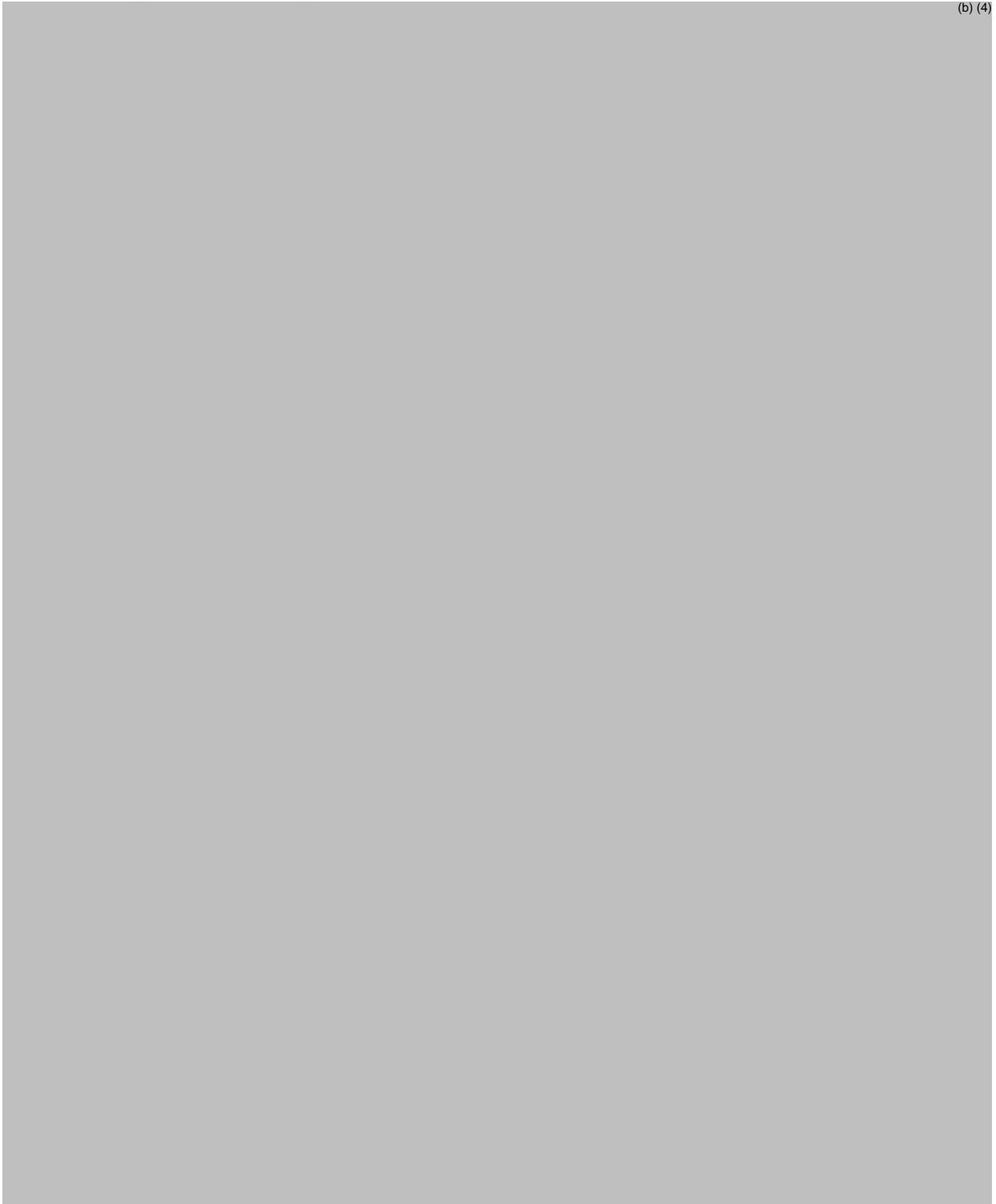
The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Component and container closure sterilization validation studies were submitted 10 October 2013
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		Submitted 10 October 2013
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	X		
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?			Not applicable
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This NDA was submitted as a rolling NDA. This filing review covers information submitted on 13 September 2013, 10 October 2013, and 20 December 2013. A

microbiology information request was sent to the applicant on 26 September 2013 and can be found in DARRTS. The response to the 26 September 2013 information request was provided on 10 October 2013. The following information request should be sent to the applicant.

Microbiology Information Request:



(b) (4)

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

/s/

JESSICA COLE
01/10/2014

BRYAN S RILEY
01/10/2014
I concur.