CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204630Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

25 January 2016

NDA: 204630

Drug Product Name
Proprietary: Pending approval
Non-proprietary: Methylene Blue Injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
09 October 2015	09 October 2015	N/A	14 January 2016

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
13 September 2013	1	17 June 2014

Applicant/Sponsor
Name: Provepharm SAS
Address: 22 rue Marc Donadille
Marseille, France 13013

U.S. Agent/Representative
Name: Clara Li
Clinipace Worldwide RSD
Address: 4840 Pearl East Circle, Suite 201E
Boulder, CO 80301

Telephone: 303-225-0980 (ext. 3024) **Fax:** 303-225-0984

Name of Reviewer: Jonathan G. Swoboda, PhD, RAC

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA amendment

2. SUBMISSION PROVIDES FOR: Response to Agency's Complete Response letter

3. MANUFACTURING SITE: CENEXI
52 rue Marcel et Jacques Gaucher
94120 Fontenay sous Bois, France

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: The subject drug product is a single-dose, sterile solution for intravenous administration [50 mg/10 mL (5 mg/mL) sealed ampoules].

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: The subject drug product is used to treat methemoglobinemia.

B. SUPPORTING/RELATED DOCUMENTS:
NDA 204630 microbiology review dated 17 June 2014.

C. REMARKS:
The subject submission is provided in eCTD format and contains responses to the Agency's Complete Response letter sent to the applicant on 10 October 2014. This submission has received orphan designation.

Filename: 204630a1.doc
Template version: OGD modified_TS_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The subject drug product is

(b) (4)

B. Brief Description of Microbiology Deficiencies – None identified.

C. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

(b) (4)

(b) (4)

B. Final Risk Assessment – No microbiology deficiencies have been identified. The safety risk is considered minimal from a sterility assurance perspective.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiology Reviewer/Jonathan G. Swoboda, PhD, RAC
Senior Microbiology Reviewer/Dupeh Palmer, PhD

C. CC Block
In Panorama

Product Quality Microbiology Assessment

This submission was previously deemed recommended for approval from a microbiology perspective (see NDA 204630 microbiology review dated 17 June 2014). The 09 October 2015 amendment contains the applicant's responses to clinical, clinical pharmacology, product quality, and labeling deficiencies conveyed in the Agency's 10 October 2014 Complete Response letter. [redacted]

Reviewer's comment: The previously calculated endotoxin dose of [redacted] EU/kg based on the proposed endotoxins specification of [redacted] EU/mL and maximum adult dose [redacted] is an acceptable endotoxins exposure level for pediatric patients (per USP<85>).

Acceptable

END

Jonathan Swoboda -S

Digitally signed by Jonathan Swoboda -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013691470, cn=Jonathan Swoboda -S
Date: 2016.01.22 20:19:06 -05'00'

Dupeh R. Palmer-ochieng -S

Digitally signed by Dupeh R. Palmer-ochieng -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000601759, cn=Dupeh R. Palmer-ochieng -S
Date: 2016.01.25 07:24:20 -05'00'

Product Quality Microbiology Review

12 June 2014

NDA: 204630/N-000

Drug Product Name
Proprietary: [redacted] (b) (4) Injection, 0.5%
Non-proprietary: Methylene Blue Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
13 September 2013	13 September 2013	20 September 2013	22 September 2013
4 March 2014	4 March 2014	N/A	N/A
25 April 2014	25 April 2014	N/A	N/A
30 May 2014	30 May 2014	N/A	N/A

Applicant/Sponsor
Name: Clinipace
Address: 4840 Pearl East Circle #201E
Boulder, CO 80301
Representative: Clara Li
Telephone: 303-225-0980

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA – Standard Review

2. SUBMISSION PROVIDES FOR: (b) (4)

3. MANUFACTURING SITE: CENEXI
52 rue Marcel et Jacques Gaucher
94120 Fontenay sous Bois
France

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Sterile Solution
- Intravenous
- 50 mg/10 mL ampoules

5. METHOD(S) OF STERILIZATION: (b) (4) (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of methemoglobinemia

B. SUPPORTING/RELATED DOCUMENTS: Not applicable

C. REMARKS: A written information request was sent to the applicant on 18 February 2014. A teleconference was held with the applicant on 1 April 2014. During the teleconference, the applicant was asked to provide validation information for container closure integrity testing. An additional information request was sent to the applicant on 9 May 2014. Responses to these information requests were provided on 4 March 2014, 25 April 2014 and 30 May 2014.

filename: N204630r1.doc

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 -
The applicant provided a description and validation data for the (b) (4) of (b) (4) Injection 0.5%.

B. Brief Description of Microbiology Deficiencies -
No deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies –
Not applicable.

D. Contains Potential Precedent Decision(s)- ☐ Yes ☒ No

III. Administrative

A. Reviewer's Signature _____
Stephen E. Langille, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block
Bryan Riley, Ph.D.
Acting Team Leader - NDMS

C. CC Block
N/A

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/s/

STEPHEN E LANGILLE
06/17/2014

BRYAN S RILEY
06/17/2014
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 204630 **Applicant:** Clinipace Worldwide **Letter Date:** 9/13/13

Drug Name: (b) (4) Injection 0.5% (Methylene Blue Injection) **NDA** Type: Priority **Stamp Date:** 9/13/13

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		Sections P.3.1, P.3.3, P.3.5, P.5, P.7, and P.8
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Sections P.3.3 and P.3.5.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Section P.5.3
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	The drug product (b) (4) The results of container closure integrity testing were not provided.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section P.5.1
7	Has the applicant submitted the results of analytical method verification studies?	X		Section P.5.3
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?		X	No such studies were requested.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The application was submitted in eCTD format. The following information request should be conveyed to the applicant:

Provide the method and results of container closure integrity testing or a reference to its location in NDA 204630.

Stephen E. Langille, Ph.D. Senior Microbiology Reviewer	10/3/13
John Metcalfe, Ph.D. Senior Microbiology Reviewer	10/3/13

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/s/

STEPHEN E LANGILLE
10/03/2013

JOHN W METCALFE
10/03/2013
I concur.