

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205098Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

12 September 2013

**NDA:** 205-098/N-000

**Drug Product Name**

**Proprietary:** Not yet determined

**Non-proprietary:** Polidocanol Injectable Microfoam

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
1 February 2013	4 February 2013	6 February 2013	7 February 2013
5 July 2013	5 July 2013	N/A	N/A
28 August 2013	28 August 2013	N/A	N/A

**Applicant/Sponsor**

**Name:** Provensis Ltd.

**Address:** 5 Fleet Place  
London, UK

**Representative:** Andreia Collier

**Telephone:** +215 317-0264

**Name of Reviewer:** Stephen E. Langille

**Conclusion:** Recommended for Approval

## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** 505(b)(2)
  2. **SUBMISSION PROVIDES FOR:** Sterility assurance package for a sterile drug product.
  3. **MANUFACTURING SITE:**

**GMP Manufacturing**  
Biocompatibles UK Ltd  
Chapman House  
Farnham Business Park  
Weydon Lane  
Farnham  
Surrey  
GU9 8QL  
UK

(b) (4)
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Sterile microfoam injection in specialized dispenser
    - Intravenous
    - 1%
  5. **METHOD(S) OF STERILIZATION:**

(b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** Treatment for moderate to severe varicose veins
- B. **SUPPORTING/RELATED DOCUMENTS:** Not applicable
- C. **REMARKS:** The application was provided in eCTD format. The following information requests were provided in the 74 day letter:

1. Please provide the (b) (4) procedure and the results of validation studies for all container closure components contacting the drug product.
2. Please provide the results of the 12/24/36-hour modified antimicrobial effectiveness testing on polidocanol referred to in section 3.2.P.2.5 of the application.

**filename:** N205098r1.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 drug product is packaged in an aluminum can which is charged with sterile oxygen gas, dispensed through a microfoam transfer unit into a syringe and administered to the patient. The drug product, oxygen gas and microfoam transfer unit are

(b) (4)

#### **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**

The following precedent was identified during review: **“Use of an unpreserved multiple dose injectable over a seven day in-use period.”** A detailed description of the precedent can be found on pp. 11-12 of this review.

### **III. Administrative**

**A. Reviewer's Signature** \_\_\_\_\_  
Stephen E. Langille, Ph.D.  
Senior Microbiology Reviewer

**B. Endorsement Block**  
John Metcalfe, Ph.D. – Senior Microbiology Reviewer

**C. CC Block**  
N/A

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/s/  
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STEPHEN E LANGILLE  
09/12/2013

JOHN W METCALFE  
09/12/2013  
I concur.

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number: 205098**

**Applicant: Provensis Ltd.**

**Letter Date: 1 Feb. 2013**

**Drug Name: Polidocanol  
Injectable Microfoam**

**NDA Type: Standard**

**Stamp Date: 4 Feb. 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		Most of this information was provided in the 3 March 2013 amendment.
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		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?		X	Not all preservative effectiveness studies were provided
9	Is this NDA fileable? If not, then describe why.	X		

**Additional Comments:**

A product quality microbiology information request was sent to the applicant on 25 February 2013 for information regarding (b)(4) validation for the drug product. The applicant provided the requested information on 5 March 2013.

During pre-NDA meetings, the applicant was advised that preservative effectiveness data was required to justify the products in-use period. The applicant provided a protocol, but no data, to support a (b)(4) in-use period for the activated canister. In addition, the applicant failed to

provide (b) (4) validation data for the container closure system. This information will be requested in the 74 day letter.

**Product Quality Comments to be provided to the applicant:**

- 1. Provide the (b) (4) procedure and the results of validation studies for all container closure components contacting the drug product.**
- 2. Provide the results of the 12/24/36 hour modified antimicrobial effectiveness test on polidocanol referred to in section 3.2.P.2.5 of the application.**

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Reviewing Microbiologist  
Stephen E. Langille Ph.D.

Date

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Bryan Riley Ph.D.  
Team Leader

Date

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/s/  
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STEPHEN E LANGILLE  
03/13/2013

BRYAN S RILEY  
03/14/2013  
I concur.