APPLICATION NUMBER:
22-466

MICROBIOLOGY REVIEW(S)
Product Quality Microbiology Review

19-FEB-2010

NDA 22-466/N-000 Amendment

Drug Product Name

Proprietary: (b) (4)
Non-proprietary: Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000 Injection

Review Number: 2

Dates of Submission(s) Covered by this Review

<table>
<thead>
<tr>
<th>Submit Date(s)</th>
<th>Received Date(s)</th>
<th>Review Request</th>
<th>Assigned to Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>09-FEB-2010</td>
<td>16-FEB-2010</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>04-FEB-2010</td>
<td>16-FEB-2010</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>28-DEC-2009</td>
<td>29-DEC-2009</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Submission History (for amendments only)

<table>
<thead>
<tr>
<th>Submit Date(s)</th>
<th>Microbiology Review #</th>
<th>Review Date(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-NOV-2008</td>
<td>1</td>
<td>07-AUG-2009</td>
</tr>
</tbody>
</table>

Applicant/Sponsor

Name: Pierrel S.p.A.
Address: 17 McIntire Drive
         Hillsborough, NJ 08844
Representative: Steven Pikulin, Ph.D. RAC
                U.S. Agent for Pierrel S.p.A
Telephone: 908-359-7791

Name of Reviewer: Steven Fong, Ph.D.

Conclusion: CMC-Microbiology recommends APPROVE.
Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA.

2. SUBMISSION PROVIDES FOR: New drug product.

3. MANUFACTURING SITE:

Articaine Hydrochloride Drug Substance:

Epinephrine Drug Substance

Articaine Hydrochloride 4% with Epinephrine 1:100000 and 1:200000 Injection Drug Product
Pierrel S.p.A.
Strada Statale Appa 46-48-1-81043
Capua (CE)
Italy

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile aqueous solution for injection containing 4% (w/v) articaine hydrochloride and either 0.002% (w/v) or 0.001% (w/v) epinephrine.

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

6. PHARMACOLOGICAL CATEGORY: Local anesthetic.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:

• The proposal was submitted as a 505(b)2 submission. The reference listed drug is Septocaine® manufactured by Septodont U.S.A. The submission proposed product sterilization by (b) (4).
• On 07-AUG-2009, a microbiology review was submitted that recommended approval with the proviso that the sponsor agree to a PMC to study the feasibility of \( (b) (4) \). In July, 2009, Agency Field Inspectors issued a FDA form 483 citation that listed 7 inspectional observations at the sponsor’s Capua, Italy, manufacturing facility. Based on this citation, the Office of Compliance recommended that approval be withheld.

• On 18-SEP-2009 the reviewer submitted a memorandum agreeing with the inspectional observations in the FDA form 483 citation, and recommended that approval be withheld until deficiencies identified in the observations were resolved. On 25-SEP-2009 a CR letter was sent to the sponsor that listed these deficiencies.

• On 29-DEC-2009 the Agency received an amendment response from the sponsor that addressed microbiology deficiencies in the 25-SEP-2009 CR letter and presented details on the \( (b) (4) \) studies that will be performed to fulfill the PMC.

• On 28-JAN-2010 the reviewer relayed a request through the project manager that the sponsor clarify responses in the 29-DEC-2009 amendment regarding \( (b) (4) \). The sponsor submitted an amendment response on 04-FEB-2010 that was marked as received 16-FEB-2010.

• On 05-FEB-2010, the reviewer relayed a request through the project manager that the sponsor clarify the PMC sterilization studies presented in the 29-DEC-2009 amendment. The sponsor submitted an amendment response on 9-FEB-2010 that was marked as received 16-FEB-2010.

filename: N022466r2.doc
Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended approvable from a microbiology quality standpoint.

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 drug product is to be sterilized by (b) (4)

B. Brief Description of Microbiology Deficiencies – None. The sponsor has adequately addressed microbiology deficiencies cited in a 25-SEP-2009 CR letter.

C. Assessment of Risk Due to Microbiology Deficiencies – No deficiencies are noted.

III. Administrative

A. Reviewer's Signature _________________________________

   Steven E. Fong, Ph.D.
   Microbiology Reviewer

B. Endorsement Block___________________________________

   James McVey
   New Drug Microbiology Team Leader

C. CC Block: N/A

8 pages have been withheld in full immediately following this page as B4 CCI/TS
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEVEN E FONG
02/19/2010
CMC-Microbiology recommends APPROVE.

JAMES L MCVEY
02/19/2010
I concur.
Pierrel S.p.A. submission NDA 22-466/N-000 proposes manufacture of Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000 Injection at the company’s Capua, Italy, production site (FDA establishment 3006999064). A 07-AUG-2009 quality microbiology review of this submission recommended approval based on the information provided in the application. On 23-JUL-2009 – 31-JUL-2009 Agency Field Investigators (microbiologist) and inspected the Capua facility and issued an FDA 483 form citing several microbiological deficiencies. Based on the field investigation report, the Office of Compliance has issued a withhold recommendation for NDA 22-466/N-000. Microbiology deficiencies cited in the field investigator’s “483” observations and the review microbiologist’s comments regarding them are presented below.

**INSPECTORATE OBSERVATION 1a**
During validation of the

**REVIEW MICROBIOLOGIST COMMENT**
Submission section 8.4 states that
INSPECTORATE OBSERVATION 1b
During validation of the

INSPECTORATE OBSERVATION 1c
Spore count verification was not performed on biological indicators to ensure the reliability of the data generated during validation of

INSPECTORATE OBSERVATION 1d
During validation of the

INSPECTORATE OBSERVATION 6
Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use and cleaning and maintenance. Specifically, the firm’s sampling booth located in the warehouse is used to sample both raw materials received in quarantine and released raw materials dispensed for use in the manufacturing operations without verification or validation of the cleaning methods performed
between products to assure removal of microbial contaminants, residual material or residual cleaning chemicals. The sampling and dispensing booth is outside the scope of the firm’s cleaning validation matrix.

**REVIEW MICROBIOLOGIST COMMENT**
The adequacy of facility equipment and cleaning methods can only be assessed by the inspector and is not subject to product microbiology review.

**INSPECTORATE OBSERVATION 7a**
Growth promotion for TSB agar used for Bioburden determination of raw material, in-process bulk solution and finished product has not been performed using Yeast, Molds, or *Brevundimonas diminuta*.

**REVIEW MICROBIOLOGIST COMMENT**
The submission states that growth promotion testing is performed for the TSB used in media fills, but, as noted, the sponsor failed to conduct this testing when performing bioburden assays. The sponsor should provide a description of the bioburden testing method that includes a growth promotion test for the culture medium.

**INSPECTORATE OBSERVATION 7b**

**REVIEW MICROBIOLOGIST COMMENT**
FDA’s guidance (page 35) on “Sterile Products Produced by (b) (4)” (2004) states, “Total combined yeast and mold count can generally be obtained by incubating at 20 to 25°C for 5 to 7 days.” This recommendation is not binding, however any temperature and medium should be validated through growth promotion studies with standard strains and representative environmental isolates. The applicant has not provided justification for the proposed incubation protocol and may submit justification or use the procedure described in the guidance. Regardless, growth promotion studies should be done.

**RECOMMENDATIONS**
Based on the information provided by the field investigator, it appears that adequate and normal laboratory controls are not utilized in the manufacture of this drug product. On this basis, the review microbiologist recommends that approval be withheld until these issues are resolved. As part of this resolution, the sponsor should provide the following additional information to the application:

1) A detailed description of the procedure used to

(b) (4)
2) Validation studies demonstrating that the cap and plunger is effective.

3) Validation studies for the

4) The SOP or a description of the SOP for validation that includes a growth promotion test and spore count for .

5) Validation studies for

6) The SOP or a description of the SOP for bioburden determination that includes a growth promotion test for the TSB agar used as a culturing medium.

7) The SOP or a description of the SOP for environmental monitoring that includes validation studies that justify the chosen incubation temperature for testing for yeasts and molds.
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22466</td>
<td>ORIG-1</td>
<td>PIERREL S.P.A.</td>
<td>ARTICAINE 4% /EPINEPHRINE 1:20000 INJ</td>
</tr>
</tbody>
</table>

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

/s/

STEVEN E FONG
09/18/2009

JAMES L MCVEY
09/18/2009
I concur.
M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 23-JAN-2009

TO: Ayanna Augustus, Regulatory Project Manager

FROM: Steven Fong, Ph.D.; Stephen Langille, Ph.D.

cc: James McVey, New Drug Microbiology team Leader
David Hussong, Ph.D., Associate Director, New Drug Microbiology Staff

SUBJECT: Microbiology Filing Review Comments for NDA 22-466

Pierrel S.p.A. stated that exposure of the product to up to a 10% loss in Epinephrine concentration and as much as a in sodium metabisulfite content. They hypothesize that

As noted in ICH Q8, the methods of sterile product manufacturing should be justified. Justification of the sterile processing should address the following concerns;

(1) .................................................. (b) (4)

(2) .................................................. (b) (4)

(3) If the studies discussed above do not resolve the .................................................. (b) (4)

Steven E. Fong, Ph.D.
Microbiology Reviewer

Stephen Langille, Ph.D.
Senior Microbiology Reviewer
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steven Fong
1/23/2009 01:04:20 PM
MICROBIOLOGIST
Submission is approved for filing from a microbiology quality standpoint. Sponsor has been asked to respond to questions regarding the use of (b)(4) (b)(4) (b)(4)

Stephen Langille
1/26/2009 08:57:51 AM
MICROBIOLOGIST
# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 22-466  
**Applicant:** Pierrel S.p.A.  
**Letter Date:** 25-NOV-2008  
**Drug Name:** Articaine 4%  
**NDA Type:** Standard  
**Stamp Date:** 03-DEC-2008

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

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>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?</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?</td>
<td>Yes</td>
<td></td>
<td>Applicant submitted (b) (4)</td>
</tr>
<tr>
<td>3. Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?</td>
<td>Yes</td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>5. Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?</td>
<td>Yes</td>
<td></td>
<td>Product contains no preservative. The resistance to microbial ingress of the container closure system (glass cartridge with cap and plunger) is to be tested</td>
</tr>
<tr>
<td>Content Parameter</td>
<td>Yes</td>
<td>No</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>-----</td>
<td>----</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>6 Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?</td>
<td>Yes</td>
<td></td>
<td>Endotoxin limits are specified for uncompounded raw materials; release limits are specified for the final, compounded product. Endotoxin levels will be measured by the compendial gel clot method (&lt;USP 51&gt;). Bioburden limits are specified for uncompounded, raw materials, and the compounded, prefILTERED drug product. Bioburden levels will be assessed with a compendial microbial limit test, &lt;USP 61&gt;. The sterility of the final, filtered product will be assessed by a compendial media fill method, &lt;USP 71&gt;. Validation studies are presented supporting the use of media fill as a sterility test.</td>
</tr>
<tr>
<td>7 Has the applicant submitted the results of analytical method verification studies?</td>
<td>Yes</td>
<td></td>
<td>Results include data for</td>
</tr>
<tr>
<td>8 Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Is this NDA fileable? If not, then describe why.</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Additional Comments: Pierrel S.p.A. notes that the reference listed drug (Septocaine®, manufactured by Septodont USA) is proposed for Articaine 4% with Epinephrine Injection because it was found to cause up to a 10% loss in Epinephrine concentration and as much as a 4% increase in sodium metabisulfite content. The possibility is cited that...

Steven E. Fong, M.S., Ph.D. Reviewing Microbiologist

Stephen Langille, Ph.D., Microbiology Secondary Reviewer
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steven Fong
1/7/2009 12:35:14 PM
MICROBIOLOGIST

Recommended for filing from a microbiology quality standpoint.

Stephen Langille
1/7/2009 12:38:03 PM
MICROBIOLOGIST