

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*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

Submit	Received	Review Request	Assigned to Reviewer
09-FEB-2010	16-FEB-2010	N/A	N/A
04-FEB-2010	16-FEB-2010	N/A	N/A
28-DEC-2009	29-DEC-2009	N/A	N/A

## Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
24-NOV-2008	1	07-AUG-2009

## 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.

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## 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:**

(b) (4)

(b) (4)

(b) (4)

**Epinephrine Drug Substance**

(b) (4)

(b) (4)

(b) (4)

**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).

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- 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). (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

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**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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22466	ORIG-1	PIERREL S.P.A.	ARTICAINE 4% /EPINEPHRINE 1:20000 INJ

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/s/

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

JAMES L MCVEY  
02/19/2010  
I concur.



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

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**DATE:** 18-SEP-2009

**TO:** Bindi Nikhar, M.D.  
Lead Medical Officer  
Division of Analgesics, Anesthetics, and Rheumatology Products  
Office of Drug Evaluation II

**FROM:** Steven Fong, Ph.D., Microbiologist  
James McVey, Microbiology Team Leader  
New Drug Microbiology Staff (NDMS)  
Office of Pharmaceutical Science

**THROUGH:** Ayanna Augustus, Ph.D., Regulatory Project Manager  
Division of Analgesics, Anesthetics, and Rheumatology Products  
Office of Drug Evaluation II

**SUBJECT:** NDA 22-466/N-000 Microbiology Review

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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 (b) (6) (microbiologist) and (b) (6) 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 (b) (4)

[REDACTED]

*REVIEW MICROBIOLOGIST COMMENT*

Submission section 8.4 states that (b) (4)

[REDACTED]

**MEMORANDUM**

[REDACTED] (b) (4)

*INSPECTORATE OBSERVATION 1b*

During validation of the [REDACTED] (b) (4)

*REVIEW MICROBIOLOGIST COMMENT*

Supporting document 7 (Amendment BA/Jul-09) [REDACTED] (b) (4)

*INSPECTORATE OBSERVATION 1c*

Spore count verification was not performed on biological indicators to ensure the reliability of the data generated during validation of [REDACTED] (b) (4)

*REVIEW MICROBIOLOGIST COMMENT*

The sponsor should provide an [REDACTED] (b) (4) validation procedure that includes determination of spore counts for challenge [REDACTED] (b) (4)

*INSPECTORATE OBSERVATION 1d*

During validation of the [REDACTED] (b) (4)

*REVIEW MICROBIOLOGIST COMMENT*

The submission does not specify what vial size was used for [REDACTED] (b) (4)  
The sponsor should provide a more detailed description of the [REDACTED] (b) (4)

*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 [REDACTED] (b) (4) manufacturing operations without verification or validation of the cleaning methods performed



## MEMORANDUM

- 2) Validation studies demonstrating that the cap and plunger [REDACTED] (b) (4) is effective.
- 3) Validation studies for the [REDACTED] (b) (4)  
[REDACTED]
- 4) The SOP or a description of the SOP for [REDACTED] (b) (4) validation that includes a growth promotion test and spore count for [REDACTED] (b) (4) [REDACTED] (b) (4).
- 5) Validation studies for [REDACTED] (b) (4)  
[REDACTED]
- 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 .

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22466	ORIG-1	PIERREL S.P.A.	ARTICAINE 4% /EPINEPHRINE 1:20000 INJ

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/s/

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STEVEN E FONG  
09/18/2009

JAMES L MCVEY  
09/18/2009  
I concur.

MEMORANDUM



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

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**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

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Pierrel S.p.A. stated that exposure of the product to (b) (4) up to a 10% loss in Epinephrine concentration and as much as a (b) (4) in sodium metabisulfite content. They hypothesize that (b) (4)

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

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/s/

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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:** Articaïne 4%  
with Epinephrine injection

**NDA Type:** Standard

**Stamp Date:** 03-DEC-2008

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?	Yes		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	Yes		Applicant submitted (b) (4)
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	Yes		(b) (4)
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?		No	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	Yes		Product contains no preservative. The resistance to microbial ingress of the container closure system (glass cartridge with cap and plunger) is to be tested

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
				by compendial methods.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	Yes		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 (<USP 51>). 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, <USP 61>. The sterility of the final, filtered product will be assessed by a compendial media fill method, <USP 71>. Validation studies are presented supporting the use of media fill as a sterility test.
7	Has the applicant submitted the results of analytical method verification studies?	Yes		Results include data for  (b) (4)
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	Yes		
9	Is this NDA fileable? If not, then describe why.	Yes		

Additional Comments: Pierrel S.p.A. notes that the reference listed drug (Septocaine®, manufactured by Septodont USA) is (b) (4) (b) (4) is proposed for Articaine 4% with Epinephrine Injection because (b) (4) was found to cause up to a 10% loss in Epinephrine concentration and as much as a (b) (4) in sodium metabisulfite content. The possibility is cited that (b) (4)

(b) (4)

(b) (4) (b) (4) (b) (4)

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

Date

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Stephen Langille, Ph.D., Microbiology Secondary Reviewer

Date

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/s/

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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