

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-466

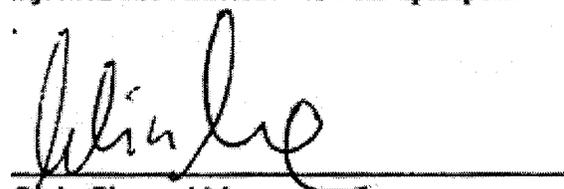
ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

1.3.5 Patent and Exclusivity

1.3.5.1 Patent Information

In the opinion and to the best knowledge of Pierrel S.p.A., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Per 21 CFR 314.50(b) and 21 CFR 314.53, patent information is submitted for the 505(b)(2) for Articaine 4% with Epinephrine 1:100000 Injection and Articaine 4% with Epinephrine 1:200000 Injection. The undersigned hereby declares that Pierrel S.p.A. does not claim any currently issued patents for Articaine 4% with Epinephrine 1:100000 Injection and Articaine 4% with Epinephrine 1:200000 Injection.



Canio Giovanni Mazzaro
CEO
Pierrel S.p.A.
Milano, Italy

October 31st 2008

Date

Form FDA 3542a is attached.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-466

NAME OF APPLICANT / NDA HOLDER

Pierrel S.p.A.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Articaine 4% with 1:100000 Epinephrine Injection and Articaine 4% with 1:200000 Epinephrine Injection

ACTIVE INGREDIENT(S)

Articaine Hydrochloride
Epinephrine Bitartrate

STRENGTH(S)

40 milligrams per mL
10 micrograms per mL or 5 micrograms per mL

DOSAGE FORM

Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
--------------------------------	-------------------------	------------------------------

d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

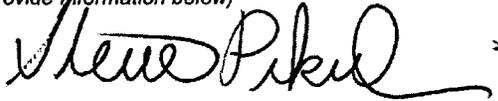
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

10/31/2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Steven Pikulin

Address

17 McIntire Drive

City/State

Hillsborough NJ

ZIP Code

08844

Telephone Number

(908) 359-7791

FAX Number (if available)

(908) 359-7540

E-Mail Address (if available)

spikulin@comcast.net

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

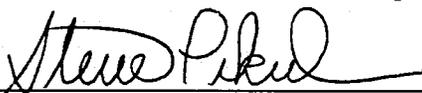
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.3.5.2 Patent/Exclusivity Certification

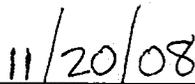
As certified in Section 1.3.5.1 of this submission, in the opinion and to the best knowledge of Pierrel S.p.A., there are no patents, owned by Pierrel or others, that claim the subject drugs.

Furthermore, per the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), the following is the current status for the Reference Listed Drugs, Septocaine® (Articaine Hydrochloride 4% with Epinephrine 1:100000 Injection and Articaine Hydrochloride 4% with Epinephrine 1:200000) Injection:

- No unexpired patents exist for either drug product presentation
- There is no unexpired marketing exclusivity for the drug product presentation with Epinephrine 1:100000
- For the drug product presentation with Epinephrine 1:200000, the marketing exclusivity expires March 30, 2009.



Steven Pikulin
US Agent for Pierrel S.p.A.



Date

A copy of the relevant pages from the Orange Book is provided in Section 1.12.11 of this submission.

EXCLUSIVITY SUMMARY

NDA # 22-466

SUPPL #

HFD # 170

Trade Name NA

Generic Name Articaine with Epinephrine

Applicant Name Pierrel, S.p.A.

Approval Date, If Known February 26, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The applicant applied for a Biowaiver which was granted. No new clinical study data was analyzed for this product.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-971 Septocaine (articaine HCl 4% with epinphrine; 1:100,000)

NDA# 22-010 Septocaine (articaine HCl 4% with epinphrine; 1:200,000)

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-971 Septocaine (articaine with 4% epinphrine; 1:100,000)

NDA# 22-010 Septocaine (articaine with 4% epinphrine; 1:200,000)

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====
Name of person completing form: Ayanna Augustus, Ph.D.
Title: Regulatory Project Manager
Date: 1/28/10

Name of Office/Division Deputy Director signing form: Rigoberto Roca, M.D.
Title: Deputy Division Director, DAARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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

/s/

AYANNA S AUGUSTUS
02/18/2010

RIGOBERTO A ROCA
02/26/2010



Debarment Certification (FD&C Act 306(k)(1))

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act ("the Act"), as amended by the Generic Drug Enforcement Act of 1992, Pierrel S.p.A. (Pierrel) hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Sections 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Carlo Giovanni Mazzaro
CEO
Pierrel S.p.A.
Milano, Italy

Date



1.3.3 Debarment Certification

As requested by the Agency, a debarment certification with the US Agent signature is provided below. The same certification signed by the responsible Pierrel official was provided in this section of the original 505(b)(2) application.

Debarment Certification (FD&C Act 306(k)(1))

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act ("the Act"), as amended by the Generic Drug Enforcement Act of 1992, Pierrel S.p.A. (Pierrel) hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Steven Pikulin
US Agent for Pierrel S.p.A.

1/5/09
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22466 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Articaine hydrochloride 4% and epinephrine 1:100,000 and 1:200,000 Dosage Form: Injection		Applicant: Pierrel S.p.A. Agent for Applicant (if applicable): Steven Pikulin, TechReg Services, Inc.
RPM:		Division: Division of Anesthesia, Analgesia, and Rheumatology Products
<p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>20-971, Septocaine® 22-010, Septocaine®</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>-pH is 3.6 whereas the RLD pH is 25 -Sodium chloride content 1.6 mg.mL, 1.0 mg/mL for RLD</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p><u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 28, 2010</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire: March 30, 2009
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	February 26, 2010
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR, September 25, 2009 AP, February 26, 2010
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	February 24, 2010
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	November 24, 2008
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	January 27, 2010
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	NA October 9, 2009, October 9, 2009
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 2/22/10; 9/24/09 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 9/15/09 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD 8/20/09
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	March 16, 2009
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Product does not trigger PREA</u> • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	12/10/08, 12/11/08, 2/3/09, 3/19/09, 3/24/09, 4/22/09, 5/21/09, 7/2/09, 7/8/09, 7/24/09, 7/27/09, 7/28/09, 8/6/09, 1/16/10, 1/15/10,

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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	1/28/10, 2/5/10, 2/18/10, 2/23/10, 2/26/10
❖ Internal memoranda, telecons, etc.	5/29/09
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg June 11, 2008
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) (<i>indicates dates</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	February 26, 2010; September 25, 2009
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	September 22, 2009
PMR/PMC Development Templates (<i>indicate total number</i>)	February 17, 2010; one PMC
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL memo/ September 22, 2009
• Clinical review(s) (<i>indicate date for each review</i>)	
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	No clinical studies submitted See CDTL memo
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁵ Filing reviews should be filed with the discipline reviews.
Version: 12/4/09

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 7, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None July 31, 2009
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 16, 2010; July 31, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 2 and 24, 2009
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 23, 2010; August 14, 2009
❖ Microbiology Reviews	<input type="checkbox"/> Not needed February 19, 2010; August 7, 2009
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None May 19, 2009

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See CMC review, August 14, 2009
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: January 14, 2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

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

/s/

AYANNA S AUGUSTUS
03/01/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-466	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Articiane Hydrochloride 4%, with Epinephrine 1:100,000 and 1:200,000 Dosage Form: injection Strengths: 40 mg/ml; 10 and 5 mg/ml epinephrine		
Applicant: Pierrel S.p.A.; Agent for Applicant (if applicable): Steven Pikulin, Ph.D., TechReg Services, Inc		
Date of Receipt: 12/29/09		
PDUFA Goal Date: 2/28/10		Action Goal Date (if different):
Proposed Indication(s): local, infiltrative or conductive anesthesia in both simple and complex dental ^{(b) (4)} procedures		

GENERAL INFORMATION

1. Is this application for a drug that is an “old” antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If “YES,” proceed to question #3.

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES NO

If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
RLD: Septocaine® Injection NDA-20-971 and 22-010	labeling
Published literature	Non-clinical and clinical data

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant has requested a bioequivalency waiver. The applicant believes the formulation differences between the RLD and the Pierrel products are insignificant and therefore no safety or efficacy issues exist.

The biowaiver was granted as of May 19, 2009.

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #6.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #6

If “YES”, list the listed drug(s) identified by name and answer question #5(c).

Articaine Hydrochloride 4% with Epinephrine (Septocaine®)

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #11.

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Septocaine®	NDA 20-971 NDA 22-010	Y Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES NO

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

9. Were any of the listed drug(s) relied upon for this application:

- a. Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: Septocaine ® Injection

- b. Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c. Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d.1.
If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

-The changes include [REDACTED] (b) (4), use of hydrochloric acid as a pH adjuster which results in a higher pH over the RLD and the applicant proposes a larger filling volume.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If “YES” and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If “NO”, proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): **There are no pharmaceutical alternatives for the applicants product.**

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): there are no unexpired patents for this product

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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/

AYANNA S AUGUSTUS
03/01/2010

Augustus, Ayanna

From: spikul@comcast.net
Sent: Friday, February 26, 2010 11:56 AM
To: Augustus, Ayanna
Subject: Revised Word labeling
Attachments: NDA22466 labeling FINAL 2-26-10.doc

Dear Ayanna:

Attached is the revised Word labeling, containing all revisions requested by the Agency. I also proofread it and corrected a couple of typos, so I am assuming it is final, but of course please let me know if I missed anything.

Also, just fyi, I received the SPL version just a few minutes ago, but I have not yet had a chance to review. Assuming there are no errors, you should receive this shortly as well.

Thanks,
Steve

6 pages of Draft Labeling has 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/

AYANNA S AUGUSTUS
02/26/2010

Augustus, Ayanna

From: spikulin@comcast.net
Sent: Tuesday, February 23, 2010 1:09 PM
To: Augustus, Ayanna
Subject: Re: Articaïne/ Carton and Container labeling

Dear Ayanna,

The requested changes were discussed with Pierrel and I can confirm that Pierrel has committed to make the requested changes to the carton label described in the e-mails below for NDA 22-466 subsequent to the approval and prior to marketing.

Thanks,
Steve

----- Original Message -----

From: "Ayanna Augustus" <Ayanna.Augustus@fda.hhs.gov>
To: "Ayanna Augustus" <Ayanna.Augustus@fda.hhs.gov>, spikulin@comcast.net
Sent: Tuesday, February 23, 2010 12:26:22 PM GMT -05:00 US/Canada Eastern
Subject: RE: Articaïne/ Carton and Container labeling

Dear Steve,

Please note no revisions to the cartridge label (other than the inclusion of the proprietary name) are needed at this time. Please disregard the requested revision. Revisions to the carton labeling remain. Please indicate ASAP that Pierrel will make the requested changes.

Regards,
Ayanna

From: Augustus, Ayanna
Sent: Monday, February 22, 2010 2:41 PM
To: 'spikulin@comcast.net'
Subject: Articaïne/ Carton and Container labeling

Dear Steve,

The Agency has the following comments regarding the cartridge and carton labels. Since it may not be possible for Pierrel to submit the revised labeling by Thursday, February 25, 2010, please indicate whether Pierrel agrees to make the listed revisions to the cartridge and carton labels.

Cartridge Labels

As currently presented, the net quantity immediately follows the established name, causing it to appear to be part of the product strength. Decrease the prominence of the net quantity statement and relocate it to appear in the top left corner of the label. In addition, revise the net quantity statement to read as '1.8 mL'.

Carton Labels

1. Ensure that the established names and product strengths are presented in the same format throughout the carton labeling:

2/25/2010

Articaine hydrochloride 4% and epinephrine 1:100,000

Articaine hydrochloride 4% and epinephrine 1:200,000

2. Increase the size of the established name so that it is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2), which states: “the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.”
3. Revise the labeling to include the ‘Rx only’ on the side panel.
4. Revise the ^{(b) (4)} statement on the principal display panel of Articaine 4% and Epinephrine 1:100,00. The strength of epinephrine per milliliter is presented as ^{(b) (4)} rather than 0.0018 mg for epinephrine 1:100,000.

Regards,
Ayanna

Ayanna Augustus, Ph.D.

*Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)*

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/

AYANNA S AUGUSTUS
02/25/2010

MEMO TO FILE

To: NDA 22-466 for Tradename (articaine HCl and epinephrine) Injection
From: Elsbeth Chikhale, Ph.D. – CMC reviewer, ONDQA, DPA I, Branch II
Through: Prasad Peri, Ph.D. – Acting Branch Chief, ONDQA, DPA I, Branch II
Date: February 23, 2010
Subject: Resubmission NDA 22-466 – CMC recommendation

Per memo to file dated September, 24, 2010, from CMC standpoint, the application was recommended NON-APPROVABLE due to the following issues:

- Microbiology deficiencies as indicated in the memo to file date September 24, 2009.
- Not acceptable recommendation from the Office of Compliance.

On September 25, 2009 a CR letter was sent to the applicant.

The applicant has responded to the CR letter in a resubmission dated December 28, 2009, followed by two submissions (responses to information requests from the Microbiology reviewer, Steven Fong, Ph.D.) dated February 4, 2010 and February 9, 2010 (both received February 16, 2010). Based on the responses to the Microbiology deficiencies and the information requests, the Microbiology review dated February 19, 2010 by Steve Fong, Ph.D., recommends APPROVAL of the NDA.

On January 14, 2010, the Office of Compliance issued an overall ACCEPTABLE recommendation for the NDA (see attached EER summary report).

Labeling review for the PI was conducted in conjunction with the clinical division, and was based on the label of the RLD, Septocaine (articaine hydrochloride and epinephrine) Injection (NDA 20-971).

The CR letter dated September 25, 2009 contained several comments from CMC and from DMEPA regarding the carton and container labels. On January 26, 2010, the applicant has submitted the following draft carton and container labels:



The same set of labels was also submitted for the higher strength, with the only difference being the strength.

The above labels have incorporated all CMC recommendations noted in the CR letter dated September 25, 2009. The carton and container labels were reviewed by Tselaine Jones Smith, PharmD, from DMEPA. The DMEPA review dated February 22, 2010 notes that the majority of DMEPA's cartridge label and carton labeling recommendations were addressed. However, added areas where the presentation of information on the labels and labeling can be clarified and improved upon to minimize the potential for medication errors were identified in DMEPA's review. DMEPA's review resulted in several additional labeling comments.

CMC conclusion and recommendation:

From CMC standpoint, the application is recommended for APPROVAL because:

- The Microbiology deficiencies have been adequately addressed (see Product Quality Microbiology review dated February 19, 2010, by Steve Fong, Ph.D.)
- The Office of Compliance has issued an ACCEPTABLE overall recommendation for this NDA (EER report dated January 14, 2010).
- The PI review was conducted and completed in coordination with the clinical division.
- The above carton and container labels have addressed all CMC comments noted in the CR letter. There are no additional CMC comments.

ATTACHMENT:

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment:	CFN: 2610211	FEI:	
	PIERREL S.P.A. STRADA STATALE APPIA 46-48 CAPUA (CE), , ITALY I81043		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-JAN-2010		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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/

ELSBETH G CHIKHALE
02/23/2010

PRASAD PERI
02/23/2010
I concur

Augustus, Ayanna

Subject: RE: NDA 22466/Additional New Information Requests

From: spikulin@comcast.net [mailto:spikulin@comcast.net]
Sent: Friday, February 19, 2010 12:36 PM
To: Augustus, Ayanna
Subject: Re: NDA 22466/Additional New Information Requests

Dear Ayanna,

It is agreed that for the labeling, the verbiage suggested by Pierrel will be removed and the most recent version provided by the Agency in the February 18 e-mail below will be incorporated.

Regarding the submission date, I am still waiting to hear back from our SPL contractor. From past history and given the magnitude of the changes, I believe the proposed February 23 submission date will be OK, but I will let you know immediately if this needs to be slightly revised.

Lastly, although Pierrel understands the reasons for the FDA position, Pierrel would also like the Agency to know that the verbiage regarding asepsis manufacturing production in the labeling was mainly proposed for ethical reasons, in order to provide the most complete information to healthcare providers in general and patients.

Best Regards,
Steve

----- Original Message -----

From: "Ayanna Augustus" <Ayanna.Augustus@fda.hhs.gov>
To: spikulin@comcast.net
Sent: Thursday, February 18, 2010 10:48:19 AM GMT -05:00 US/Canada Eastern
Subject: RE: NDA 22466/Additional New Information Requests

Dear Steve,

Regarding the proposed changes to the package insert, the Division believes the (b) (4)

[REDACTED] In addition, the division believes the original language proposed for Contraindications section of the label should remain. Enclosed is a copy of the final draft PI. If Pierrel does not have any additional changes to the PI, please submit final product labeling to the NDA in WORD and SPL format. Please indicate if you will be able to do so by Tuesday, February 23, 2010.

Regards,
Ayanna

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/

AYANNA S AUGUSTUS
02/22/2010

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor will subject the drug product to various (b) (4), and evaluate the effects of these parameters on short and long term stability as detailed in item 2. It can be noted that the sponsor has already demonstrated that an (b) (4) equivalent does not significantly alter short term product stability. Epinephrine content decreased slightly (b) (4) and there was a slight (b) (4) increase in pH, but these changes were within accepted limits. Stability studies are necessary to determine whether the product remains within specifications over the proposed two year shelf life. The sponsor is recommended to examine short and long term stability following varying (b) (4) treatment regimens. These may include (b) (4) equivalents less than (b) (4) that nonetheless provide an acceptable level of sterility assurance.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/

AYANNA S AUGUSTUS
02/17/2010

LARISSA LAPTEVA
02/17/2010



FDA Center for Drug Evaluation and Research
 Division of Anesthesia, Analgesia, and Rheumatology Products
 10903 New Hampshire Avenue, Silver Spring, MD 20993

MEMO TO FILE

NDA number: 22-466
Sponsor: Pierrel S.p.A.
 Via A. Saffi, 25
 20123 Milan, Italy
U.S. Agent: TechReg Services, Inc.
 Steven Pikulin
 17 McIntyre Drive
 Hillsborough, NJ 08844
Submission Type: NDA resubmission
Supporting Doc Number: 10
Submission Date/Receipt: December 28, 2009 / December 29, 2009
Drug Substance: Articaine hydrochloride 4% with
 epinephrine 1:100000 and 1:200000
Reviewer name: Carlic K. Huynh, Ph.D.
Supervisor name: R. Daniel Mellon, Ph.D.
Division name: Division of Anesthesia, Analgesia, and
 Rheumatology Products
Review completion date: February 16, 2010

Recommendation: The Sponsor has provided adequate data to conclude that (b) (4) and (b) (4) are not mutagenic. The Sponsor has addressed and resolved the previously recommended postmarketing commitment as part of the complete response. From a nonclinical pharmacology toxicology perspective, NDA 22-466 may be approved with no post marketing studies required at this time.

Background/Prior Regulatory History:

On September 25, 2009, the Sponsor was sent a complete response letter from the Agency that included the following Postmarketing Commitment (PMC):

- Investigate the potential for optimizing the sensitivity of the analytical methodology with regard to (b) (4) (b) (4) to determine if either of these impurities is present in the drug substance at levels that would exceed (b) (4). If these impurities exceed (b) (4) then conduct the following studies:**

- a. **Conduct an in vitro bacterial reverse mutation assay (Ames assay) with the isolated** (b) (4) **tested up to the limit dose of the assay.**
- b. **Conduct an in vitro bacterial reverse mutation assay (Ames assay) with the isolated** (b) (4) **tested up to the limit dose of the assay.**

To address the above PMC issue, the Sponsor has submitted in vitro bacterial reverse mutation assays (Ames Assay) for these impurities (b) (4) in this NDA resubmission.

Genetic Toxicology Study #1:

Study title: *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay with (b) (4)

Key findings:

- This assay is deemed valid.
- The bacterial tester strains of *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2 uvrA were incubated with 3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate (b) (4)
- (b) (4) is not mutagenic in the in vitro bacterial reverse mutation assay.

Study no.: 1303802

Conducting laboratory and location: (b) (4)

Date of study initiation: November 18, 2009

GLP compliance: Yes. Signature provided.

QA reports: yes (X) no (), signature provided on December 9, 2009.

Drug, lot #, and % purity: (b) (4) 100% purity

Note: (b) (4) is also known as (b) (4) The chemical name of (b) (4) is (b) (4) The CAS number is (b) (4)

Methods

Strains/species/cell line:

The bacterial tester strains used were *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2 uvrA. The S9 mix was derived from rat liver and was induced by phenobarbital/β-naphthoflavone.

Doses used in definitive study:

The doses used in the definitive study were 3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate (b) (4)

Basis of dose selection:

The highest dose tested was 5000 µg/plate (b) (4). The 5000 µg/plate dose of (b) (4) was the maximum solubility of the test compound in the vehicle.

Negative controls:

The negative control was the vehicle, dimethyl sulfoxide (DMSO), with and without S9 activation.

Positive controls:

With S9 activation, the positive control was 2-aminoanthracene (2-AA). Without S9 activation, the positive control was sodium azide (NaN₃), 4-nitro-*o*-phenylate-diamine (4-NOPD), or methyl methanesulfonate (MMS).

Incubation and sampling times:

(b) (4) in vehicle, vehicle alone, or positive control was pre-incubated with the bacteria with and without S9 mix was pre-incubated at 37°C for 60 min. After pre-incubation, the overlay agar at 45°C was added. The mixture was poured on selective agar plates. After the overlay solidified, the plates were inverted and incubated at 37°C for at least 48 hrs in the dark. Following incubation, the plates were counted.

ResultsStudy validity:

The study is considered valid for the following reasons: 1) the appropriate controls were used; 2) the appropriate strains were tested; 3) the positive control substances produced reliable positive results; 4) the highest concentration of (b) (4) tested reached the maximum recommended concentration of 5,000 µg/plate; and 5) there was no evidence for a dose dependent increase in revertants following drug treatment.

Study outcome:

Table 1 is a summary of the results of the first of two experiments testing (b) (4)

Table 1: Summary of Results Experiment I

Metabolic Activation	Test Group	Dose Level (per plate)	Revertant Colony Counts (Mean ±SD)				
			TA 1535	TA 1537	TA 98	TA 100	WP2 uvrA
Without Activation	DMSO Untreated (b) (4)		15 ± 2	9 ± 3	22 ± 6	91 ± 5	55 ± 2
			14 ± 3	13 ± 5	32 ± 9	102 ± 3	58 ± 3
		3 µg	15 ± 7	12 ± 3	24 ± 4	103 ± 4	53 ± 4
		10 µg	16 ± 4	14 ± 1	31 ± 2	101 ± 6	54 ± 7
		33 µg	16 ± 4	13 ± 3	28 ± 1	102 ± 15	55 ± 2
		100 µg	16 ± 3	11 ± 5	25 ± 4	101 ± 3	49 ± 7
		333 µg	14 ± 1	11 ± 4	26 ± 5	102 ± 31	48 ± 15
		1000 µg	12 ± 3	12 ± 4	16 ± 6	92 ± 15	39 ± 5
		2500 µg	14 ± 3	10 ± 3	12 ± 5	63 ± 8	12 ± 3
		5000 µg	14 ± 1	5 ± 3	7 ± 5	48 ± 4	3 ± 3
		NaN3 10 µg	1596 ± 71		265 ± 8	2040 ± 95	
		4-NOPD 10 µg					
		4-NOPD 50 µg		104 ± 15			
		MMS 3.0 µL					1203 ± 44
		With Activation	DMSO Untreated (b) (4)		17 ± 5	12 ± 4	41 ± 1
	18 ± 4			17 ± 3	49 ± 2	120 ± 2	71 ± 4
3 µg	20 ± 4			18 ± 2	37 ± 5	117 ± 17	65 ± 6
10 µg	23 ± 4			19 ± 2	41 ± 6	123 ± 4	64 ± 3
33 µg	16 ± 2			18 ± 4	37 ± 1	119 ± 19	69 ± 11
100 µg	28 ± 8			20 ± 3	38 ± 7	116 ± 18	53 ± 5
333 µg	21 ± 7			19 ± 5	33 ± 12	102 ± 8	63 ± 5
1000 µg	15 ± 2			11 ± 2	26 ± 14	84 ± 7	38 ± 5
2500 µg	14 ± 6			14 ± 6	20 ± 3	54 ± 3	25 ± 2
5000 µg	12 ± 3 ^R			13 ± 1 ^R	9 ± 1 ^R	33 ± 12 ^R	11 ± 2 ^R
2-AA 2.5 µg	393 ± 48			341 ± 36	2458 ± 196	2343 ± 17	
2-AA 10.0 µg							356 ± 32

Key to Positive Controls

Key to Plate Postfix Codes

NaN3 sodium azide
 2-AA 2-aminoanthracene
 4-NOPD 4-nitro-o-phenylene-diamine
 MMS methyl methane sulfonate

R Reduced background growth

As shown in Table 1, each of the tester strains (TA 1535, TA 1537, TA 98, TA 100, and WP2 uvrA), when incubated with the range of concentrations of (b) (4) (3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate) and in the absence or presence of metabolic activation, did not have an increase in the revertant colony counts over the positive control.

Table 2 is a summary of the results of the second experiment testing (b) (4)

Table 2: Summary of Results Experiment II

Metabolic Activation	Test Group	Dose Level (per plate)	Revertant Colony Counts (Mean ±SD)					
			TA 1535	TA 1537	TA 98	TA 100	WP2 uvrA	
Without Activation	DMSO Untreated		13 ± 5	16 ± 3	26 ± 2	111 ± 28	44 ± 2	
		(b) (4)	15 ± 8	12 ± 2	37 ± 13	138 ± 22	54 ± 16	
	(b) (4)	3 µg	12 ± 4	14 ± 4	26 ± 6	98 ± 5	44 ± 1	
		10 µg	17 ± 3	12 ± 2	31 ± 2	94 ± 7	51 ± 8	
		33 µg	14 ± 4	14 ± 6	25 ± 3	108 ± 10	44 ± 4	
		100 µg	15 ± 6	13 ± 1	23 ± 4	108 ± 13	52 ± 4	
		333 µg	16 ± 8	12 ± 3	16 ± 6	73 ± 6	34 ± 9	
		1000 µg	14 ± 2	13 ± 4	15 ± 3	75 ± 10	21 ± 6	
		2500 µg	13 ± 2	12 ± 7	14 ± 6	79 ± 11	13 ± 2	
		5000 µg	11 ± 1	3 ± 3	3 ± 3	44 ± 3	3 ± 3	
		NaN3	10 µg	1484 ± 179			1604 ± 199	
		4-NOPD	10 µg				412 ± 27	
		4-NOPD	50 µg	95 ± 7				
		MMS	3.0 µL				552 ± 52	
		With Activation	DMSO Untreated		17 ± 10	24 ± 2	48 ± 7	115 ± 23
(b) (4)	13 ± 7			22 ± 3	44 ± 4	154 ± 43	54 ± 11	
(b) (4)	3 µg		18 ± 2	20 ± 7	46 ± 3	83 ± 19	47 ± 3	
	10 µg		20 ± 3	23 ± 7	37 ± 2	114 ± 12	52 ± 10	
	33 µg		21 ± 5	17 ± 2	42 ± 4	126 ± 8	52 ± 8	
	100 µg		17 ± 2	19 ± 3	37 ± 4	129 ± 20	53 ± 2	
	333 µg		15 ± 3	17 ± 5	37 ± 4	91 ± 23	35 ± 2	
	1000 µg		17 ± 3	16 ± 1	23 ± 2	79 ± 8	26 ± 4	
	2500 µg		12 ± 6	14 ± 2	21 ± 2	60 ± 9	19 ± 5	
	5000 µg		11 ± 6 ^R	10 ± 4 ^R	8 ± 1 ^R	21 ± 1 ^R	8 ± 6 ^R	
	2-AA		2.5 µg	260 ± 34	164 ± 14	1351 ± 269	1675 ± 90	
2-AA	10.0 µg				393 ± 52			

Key to Positive Controls

Key to Plate Postfix Codes

NaN3	sodium azide	R	Reduced background growth
2-AA	2-aminoanthracene		
4-NOPD	4-nitro-o-phenylene-diamine		
MMS	methyl methane sulfonate		

As shown in Table 2, each of the tester strains (TA 1535, TA 1537, TA 98, TA 100, and WP2 uvrA), when incubated with the range of concentrations of (b) (4) (3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate) and in the absence or presence of metabolic activation, did not have an increase in the revertant colony counts over the positive control.

Table 3 is the historical control data.

Table 3: Historical Control Data

Strain		without S9 mix				with S9 mix			
		Mean	SD	Min	Max	Mean	SD	Min	Max
TA 1535	Solvent control	17	5.17	(b) (4)	(b) (4)	21	5.82	(b) (4)	(b) (4)
	Negative control	17	5.33			20	6.23		
	Positive control	2024	315.78			294	140.02		
TA1537	Solvent control	13	3.12			17	3.90		
	Negative control	13	3.38			18	4.05		
	Positive control	116	30.52			204	69.54		
TA 98	Solvent control	30	5.59			39	6.34		
	Negative control	31	5.45			39	6.53		
	Positive control	489	169.76			1455	463.01		
TA 100	Solvent control	130	18.79			155	22.54		
	Negative control	139	17.30			147	21.78		
	Positive control	2160	342.67			1839	621.27		
WP2uvrA	Solvent control	49	8.02			60	8.76		
	Negative control	49	8.58			60	8.71		
	Positive control	986	481.97			414	158.56		

Mean = mean value of revertants/plate

SD = standard deviation

Min = minimal value/Max = maximal value

It is noted that the revertant colony counts from Tables 1 and 2 are far below the positive control ranges in the historical control (shown in Table 3) for any of the tester strains with and without metabolic activation.

According to the data from Tables 1-3, (b) (4) is not mutagenic.

Genetic Toxicology Study #2:

Study title: *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay with (b) (4)

Key findings:

- This assay is deemed valid.
- The bacterial tester strains of *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2 uvrA were incubated with 3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate (b) (4)
- (b) (4) is not mutagenic in the in vitro bacterial reverse mutation assay.

Study no.: 1303801

Conducting laboratory and location:

(b) (4)

Date of study initiation:

November 18, 2009

GLP compliance: Yes. Signature provided.**QA reports:** yes (X) no (), signature provided on December 9, 2009.**Drug, lot #, and % purity:** (b) (4), 100% purity

Note: (b) (4) is also known as (b) (4). The chemical name of (b) (4) is (b) (4). The CAS number for (b) (4) has not been assigned.

MethodsStrains/species/cell line:

The bacterial tester strains used were *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2 uvrA. The S9 mix was derived from rat liver and was induced by phenobarbital/ β -naphthoflavone.

Doses used in definitive study:

The doses used in the definitive study were 3, 10, 33, 100, 333, 1000, 2500, and 5000 μ g/plate (b) (4).

Basis of dose selection:

The highest dose tested was 5000 μ g/plate (b) (4). The 5000 μ g/plate dose of (b) (4) was the maximum solubility of the test compound in the vehicle.

Negative controls:

The negative control was the vehicle, dimethyl sulfoxide (DMSO), with and without S9 activation.

Positive controls:

With S9 activation, the positive control was 2-aminoanthracene (2-AA). Without S9 activation, the positive control was sodium azide (NaN_3), 4-nitro-*o*-phenylate-diamine (4-NOPD), or methyl methanesulfonate (MMS).

Incubation and sampling times:

(b) (4) in vehicle, vehicle alone, or positive control was pre-incubated with the bacteria with and without S9 mix was pre-incubated at 37°C for 60 min. After pre-incubation, the overlay agar at 45°C was added. The mixture was poured on selective agar plates. After the overlay solidified, the plates were inverted and incubated at 37°C for at least 48 hrs in the dark. Following incubation, the plates were counted.

Results

Study validity:

The study is considered valid for the following reasons: 1) the appropriate controls were used; 2) the appropriate strains were tested; 3) the positive control substances produced reliable positive results; 4) the highest concentration of (b) (4) tested reached the maximum recommended concentration of 5,000 µg/plate; and 5) there was no evidence for a dose dependent increase in revertants following drug treatment.

Study outcome:

Table 4 is the summary of results from the first of two experiments testing (b) (4)

Table 4: Summary of Results Experiment I

Metabolic Activation	Test Group	Dose Level (per plate)	Revertant Colony Counts (Mean ±SD)					
			TA 1535	TA 1537	TA 98	TA 100	WP2 uvrA	
Without Activation	DMSO Untreated		13 ± 1	13 ± 1	33 ± 5	98 ± 15	51 ± 3	
		(b) (4)	11 ± 4	16 ± 5	30 ± 7	107 ± 8	60 ± 9	
	(b) (4)	3 µg	14 ± 2	12 ± 2	26 ± 2	96 ± 5	49 ± 3	
		10 µg	15 ± 1	9 ± 1	29 ± 7	109 ± 8	52 ± 10	
		33 µg	13 ± 4	12 ± 2	26 ± 2	92 ± 8	50 ± 7	
		100 µg	15 ± 3	11 ± 1	28 ± 2	103 ± 9	43 ± 1	
		333 µg	15 ± 3	10 ± 4	28 ± 6	112 ± 20	49 ± 6	
		1000 µg	11 ± 4	10 ± 3	28 ± 3	110 ± 11	39 ± 4	
		2500 µg	12 ± 2 ^P	5 ± 1 ^{MRP}	20 ± 4 ^{PMR}	110 ± 10 ^P	35 ± 8 ^P	
		5000 µg	8 ± 1 ^{PMR}	5 ± 1 ^{PMR}	18 ± 4 ^{PMR}	91 ± 11 ^{PM}	14 ± 5 ^{PMR}	
		NaN3	10 µg	1785 ± 40			1871 ± 22	
		4-NOPD	10 µg			282 ± 23		
		4-NOPD	50 µg		92 ± 3			
		MMS	3.0 µL					1130 ± 38
		With Activation	DMSO Untreated		15 ± 1	20 ± 2	39 ± 6	107 ± 7
(b) (4)	18 ± 3			14 ± 2	43 ± 7	110 ± 7	63 ± 2	
(b) (4)	3 µg		16 ± 1	14 ± 3	39 ± 3	115 ± 4	66 ± 13	
	10 µg		18 ± 3	16 ± 3	43 ± 5	117 ± 8	60 ± 12	
	33 µg		19 ± 3	16 ± 1	40 ± 2	137 ± 11	68 ± 3	
	100 µg		18 ± 4	16 ± 3	41 ± 7	125 ± 21	63 ± 3	
	333 µg		16 ± 5	19 ± 3	36 ± 7	116 ± 4	52 ± 5	
	1000 µg		17 ± 3	15 ± 1	36 ± 2	115 ± 14	48 ± 6	
	2500 µg		17 ± 2 ^P	11 ± 1 ^{PMR}	23 ± 3 ^{PMR}	119 ± 5 ^P	40 ± 4 ^P	
	5000 µg		9 ± 3 ^{PMR}	11 ± 1 ^{PMR}	15 ± 4 ^{PMR}	96 ± 18 ^{PM}	12 ± 2 ^{PMR}	
	2-AA		2.5 µg	336 ± 25	354 ± 54	2158 ± 257	2728 ± 75	
	2-AA		10.0 µg					404 ± 29

Key to Positive Controls Key to Plate Postfix Codes

NaN3	sodium azide	P	Precipitate
2-AA	2-aminoanthracene	M	Manual count
4-NOPD	4-nitro-o-phenylene-diamine	R	Reduced background growth
MMS	methyl methane sulfonate		

As shown in Table 4, each of the tester strains (TA 1535, TA 1537, TA 98, TA 100, and WP2 uvrA), when incubated with the range of concentrations of (b) (4) 3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate), did not have an increase in the revertant colony counts over the positive control, with or without metabolic activation.

Table 5 is the summary of results from the second experiment testing (b) (4)

Table 5: Summary of Results Experiment II

Metabolic Activation	Test Group	Dose Level (per plate)	Revertant Colony Counts (Mean ±SD)				
			TA 1535	TA 1537	TA 98	TA 100	WP2 uvrA
Without Activation	DMSO Untreated (b) (4)		16 ± 1	13 ± 4	26 ± 3	120 ± 5	46 ± 9
			17 ± 3	11 ± 3	31 ± 11	131 ± 11	46 ± 4
		3 µg	15 ± 1	11 ± 4	24 ± 3	102 ± 3	43 ± 4
		10 µg	16 ± 1	12 ± 5	30 ± 4	110 ± 5	46 ± 7
		33 µg	17 ± 3	12 ± 4	25 ± 6	115 ± 8	45 ± 11
		100 µg	15 ± 2	13 ± 2	24 ± 4	107 ± 2	48 ± 3
		333 µg	14 ± 1	15 ± 1	25 ± 2	110 ± 17	43 ± 2
		1000 µg	11 ± 1	11 ± 2	27 ± 5	109 ± 7	47 ± 9
		2500 µg	7 ± 0	16 ± 1	25 ± 4	107 ± 11	32 ± 6
		5000 µg	7 ± 2 ^{PMR}	8 ± 2 ^{PMR}	18 ± 3 ^{PMR}	82 ± 10 ^{PMR}	11 ± 2 ^{PMR}
		NaN3 10 µg	1835 ± 49		350 ± 21	1936 ± 64	
		4-NOPD 10 µg		80 ± 2			
		4-NOPD 50 µg					
		MMS 3.0 µL					256 ± 29
	With Activation	DMSO Untreated (b) (4)		23 ± 1	18 ± 2	38 ± 9	133 ± 6
			18 ± 3	19 ± 2	44 ± 1	162 ± 9	60 ± 8
3 µg			18 ± 6	18 ± 3	45 ± 9	127 ± 30	69 ± 3
10 µg			20 ± 5	20 ± 2	37 ± 6	136 ± 7	63 ± 15
33 µg			18 ± 3	18 ± 2	37 ± 4	126 ± 8	62 ± 17
100 µg			22 ± 4	17 ± 3	39 ± 8	117 ± 6	62 ± 4
333 µg			19 ± 2	19 ± 2	35 ± 7	120 ± 16	59 ± 6
1000 µg			19 ± 5	15 ± 6	33 ± 3	113 ± 6	51 ± 6
2500 µg			14 ± 5	14 ± 2	37 ± 7	129 ± 8	36 ± 2
5000 µg			8 ± 2 ^{PMR}	11 ± 1 ^{PMR}	20 ± 3 ^{PMR}	93 ± 13 ^{PMR}	16 ± 7 ^{PMR}
	2-AA 2.5 µg	291 ± 17	203 ± 7	1771 ± 15	2089 ± 99		
	2-AA 10.0 µg					431 ± 19	
Key to Positive Controls			Key to Plate Postfix Codes				
NaN3	sodium azide		P	Precipitate			
2-AA	2-aminoanthracene		M	Manual count			
4-NOPD	4-nitro-o-phenylene-diamine		R	Reduced background growth			
MMS	methyl methane sulfonate						

As shown in Table 5, each of the tester strains (TA 1535, TA 1537, TA 98, TA 100, and WP2 uvrA), when incubated with the range of concentrations of (b) (4) (3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate), did not have an increase in the revertant colony counts over the positive control, with or without metabolic activation.

Table 6 is the historical control data.

Table 6: Historical Control Data

Strain		without S9 mix				with S9 mix			
		Mean	SD	Min	Max	Mean	SD	Min	Max
TA 1535	Solvent control	17	5.17		(b) (4)	21	5.82		(b) (4)
	Negative control	17	5.33		20	6.23			
	Positive control	2024	315.78		294	140.02			
TA1537	Solvent control	13	3.12		17	3.90			
	Negative control	13	3.38		18	4.05			
	Positive control	116	30.52		204	69.54			
TA 98	Solvent control	30	5.59		39	6.34			
	Negative control	31	5.45		39	6.53			
	Positive control	489	169.76		1455	463.01			
TA 100	Solvent control	130	18.79		155	22.54			
	Negative control	139	17.30		147	21.78			
	Positive control	2160	342.67		1839	621.27			
WP2uvrA	Solvent control	49	8.02	60	8.76				
	Negative control	49	8.58	60	8.71				
	Positive control	986	481.97	414	158.56				

Mean = mean value of revertants/plate

SD = standard deviation

Min = minimal value/Max = maximal value

It is noted that the revertant colony counts from Tables 4 and 5 are far below the positive control ranges in the historical control (shown in Table 6) for any of the tester strains with and without metabolic activation.

According to the data from Tables 4-6, (b) (4) is not mutagenic.

Conclusions:

From the results of the in vitro bacterial reverse mutation assays conducted by the Sponsor, it is concluded that (b) (4) are not mutagenic.

The Sponsor has fulfilled concerns from the nonclinical pharmacology toxicology review team regarding proposed postmarketing commitments during the first review cycle for this NDA that was addressed in the complete response letter from September 25, 2009. The Sponsor has fulfilled the concerns of the nonclinical pharmacology toxicology review team by conducting in vitro bacterial reverse mutation assays on both impurities (b) (4). This NDA may be approved without PMCs.

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/

CARLIC K HUYNH
02/16/2010

RICHARD D MELLON
02/16/2010
I concur.

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Friday, February 05, 2010 4:49 PM
To: 'spikulin@comcast.net'
Subject: NDA 22466/Additional New Information Requests
Importance: High

Hi Steve,

Please note the following new information requests. Please have an electronic response sent to me by COB, Tuesday, February 9, 2009, complete with cover letter and 356h form.

Regards,
 Ayanna

1. Regarding your proposal for conducting (b) (4) feasibility studies:
 - a. It would be preferable if the studies were conducted with (b) (4) processed product in which bioburden has effectively been eliminated. This would increase the chance that short, bioburden-based (b) (4) could be found that effect sterilization without adverse influence on product quality. Are the proposed studies to be performed with (b) (4) processed product?
 - b. Please provide the calculated F_0 's for the proposed sterilization parameters (b) (4)
 - c. Please provide the calculated sterilization assurance level (SAL) for the proposed sterilization parameters based on estimated pre-sterilization bioburden levels. (The bioburden would be zero if the product is (b) (4) prior to sterilization.)
2. Although document PCV-IM-030-09 represents a protocol for (b) (4) and does not contain procedures for (b) (4) testing, the placement of (b) (4) during (b) (4) validation is nonetheless requested. Please provide a description of (b) (4) placement and/or the relevant SOP.

From: spikulin@comcast.net [mailto:spikulin@comcast.net]
Sent: Thursday, February 04, 2010 4:03 PM
To: Augustus, Ayanna
Cc: spikulin
Subject: Re: NDA 022466: New Information Requests

Dear Ayanna,

Attached is a pdf file with the cover letter and 356h. Please confirm receipt.

Would you like me to send you the originals by FedEx?

Please let me know if there are any other questions.

Thanks,

2/16/2010

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/

AYANNA S AUGUSTUS
02/16/2010

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Thursday, January 28, 2010 5:58 PM
To: 'spikulin@comcast.net'
Subject: NDA 022466: New Information Requests

Importance: High

Attachments: NDA22466 labeling 1-26-10.doc

Dear Steve,

Enclosed you'll find draft labeling for articaine in tracked changes mode. Please review the changes and submit final clean labeling in Word format. If you have any additional changes, please provide a copy of the label in tracked changes mode. In addition please note the following information requests:

The post-marketing commitment requires the sponsor to conduct studies for assessing the long and short term stability of (b) (4) product. The goal of these studies is to determine (b) (4) (b) (4) that do not cause product degradation beyond allowed specifications immediately after treatment and over a two year (room temperature) shelf life. The 28-DEC-2009 complete response resubmission does not adequately address this commitment. The sterilization parameters are not provided, and long term storage condition testing is only proposed for (b) (4)

- 1) Provide details on the (b) (4) that will be tested. Note that the protocol sent via email on January 22, 2010 does not adequately describe the sterilization parameters that will be tested.
- 2) Provide a commitment to generate ICH Q1A(R2) stability data over a **24 month period** using long term storage conditions. In addition, provide a revised submission date for the final study report for this postmarketing study.

In regards to the response to comment 3 in the Complete Response submission dated 12.28.09:

- 3) Provide a description of the positive controls and negative controls used for the endotoxin removal studies presented in RCV-IM-008-09, section 13.4. Typically, positive controls would consist of endotoxin-challenged items that are not subjected to (b) (4). Negative controls would consist of nonchallenged items. The endotoxin reduction data presented in RCV-IM-008-09 is not acceptable without data from the controls.
- 4) Provide the identity of material used as an endotoxin challenge.

In regards to the response to comment 4:

- 5) Provide a justification that the (b) (4) presented in document PCV-IM-030-09 represents a worst case load scenario.
- 6) Provide the location of the (b) (4) in the (b) (4). This information was requested in comment 4 but was not responded to.

7) (b) (4)

In regards to the response to comment 5,

8) Provide a description of the positive and negative controls used for the endotoxin removal studies.

Please provide a response by COB, Wednesday, February 3, 2010. Also please email me your responses as well as submit them formally to the NDA.

Regards,

Ayanna



NDA22466 labeling
1-26-10.doc

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)

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/

AYANNA S AUGUSTUS
02/02/2010

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Friday, January 15, 2010 11:18 AM
To: 'Steven Pikulin'
Subject: NDA 22466/Information Requests

Importance: High

Dear Steve,

I hope to have information on the classification of your resubmission by early next week. In the meantime, please provide the following by COB, Tuesday, January 19, 2009.

1. Revised carton and cartridge labels with the word "Tradename" as the place holder rather than (b) (4) which is not the approved name for the product. Please email a copy to me and submit e-copies to the NDA.
2. Provide the protocol for the PMC study designed to identify suitable (b) (4) conditions, detailing the specific (b) (4) conditions that will be tested. Please email me a copy of the protocol as well as submitting this formally to the NDA.
3. Please provide a month, date and year for submission of the final study reports for the PMC studies to identify the suitable (b) (4) conditions and the postmarketing study that will generate stability data for selected (b) (4) conditions.

Regards,
Ayanna

*Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)*

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/

AYANNA S AUGUSTUS
02/02/2010



NDA 022466

ACKNOWLEDGE CLASS 1 COMPLETE RESPONSE

Pierrel S.p.A.
c/o TechReg Services, Inc
17 McIntire Drive
Hillsborough, NJ 08844

Attention: Steven Pikulin, Ph.D., RAC
US Agent for Pierrel S.p.A

We acknowledge receipt on December 29, 2009, of your December 28, 2009, resubmission to your new drug application for Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000; Injection.

We consider this a complete, Class 1 response to our September 25, 2009, action letter. Therefore, the user fee goal date is February 28, 2010.

If you have any questions, contact, Ayanna Augustus, Ph.D., Regulatory Project Manager, at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/

PARINDA JANI
01/20/2010



NDA 022466

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Pierrel S.p.A.
c/o TechReg Services, Inc
17 McIntire Drive
Hillsborough, New Jersey 08844

ATTENTION: Steven Pikulin, Ph.D., RAC
President, TechReg Services

Dear Dr. Pikulin:

Please refer to your New Drug Application (NDA) dated November 24, 2008, received November 25, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000 Injection.

We also refer to your July 11, 2009, correspondence, received July 14, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

The proposed proprietary name, (b) (4) contains the United States Adopted Name (USAN) stem '(b) (4)'. This stem is used by USAN to indicate a local anesthetic product. Although (b) (4) is a local anesthetic drug product and its use is consistent with the intended USAN meaning, the USAN Council uses this stem for established names only.

The use of stems in proprietary names can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the risk of confusion among those drugs. This confusion may compromise patient safety. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names. We recommend you screen potential proprietary names against the USAN stem list and eliminate those that incorporate USAN stems.

Additionally, the proposed proprietary name (b) (4) was found to be orthographically and phonetically similar to the proprietary name, Carbocaine. The orthographic similarities of this name pair stem from the similar length of the name (9 letters vs. 10 letters), identical beginning 'Ca' and ending 'caine' letters. Although the lower case 'b' and the lower case 'p' usually represent an upstroke in Carbocaine and down stroke in (b) (4) respectively,

if either expression is blunted, these orthographic differences may not be sufficient to differentiate the two proprietary names.

Phonetically, there are minimal differences between the two proprietary names especially since they share identical beginning and ending sounds. Additionally, the infixes 'bo' vs. 'pa' can be phonetically similar. In addition to the orthographic and phonetic similarity the products share similar product characteristics such as similar indication of use and same setting of use. The appearance of the product is similar as well. Both are available in the same cartridge size (1.8 mL) and look similar once a cartridge has been loaded into an injector.

Although the products have different strengths and dosing recommendations, the strengths and/or doses may not be written in the chart or on an order prior to use when they can be used to differentiate the two products. Thus, dental staff may only be directed to procure and prepare 'X' number of Carbocaine/^{(b) (4)} cartridges for the dental procedure. Given the similarity of this name pair and the similarity of the product characteristics, our analysis indicates that medication errors are likely to occur with these products if the name ^{(b) (4)} is approved.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Bola Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Ayanna Augustus at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/

CAROL A HOLQUIST
10/09/2009

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-466	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Articiane Hydrochloride 4%, with Epinephrine 1:100,000 and 1:200,000 Dosage Form: injection Strengths: 40 mg/ml; 10 and 5 mg/ml epinephrine		
Applicant: Pierrel S.p.A.; Agent for Applicant (if applicable): Steven Pikulin, Ph.D., TechReg Services, Inc		
Date of Receipt: 11/25/08		
PDUFA Goal Date: 9/25/09		Action Goal Date (if different):
Proposed Indication(s): local, infiltrative or conductive anesthesia in both simple and complex dental ^{(b) (4)} procedures		

GENERAL INFORMATION

1. Is this application for a drug that is an “old” antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If “YES,” proceed to question #3.

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES NO

If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
RLD: Septocaine® Injection NDA-20-971 and 22-010	labeling
Published literature	Non-clinical and clinical data

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant has requested a bioequivalency waiver. The applicant believes the formulation differences between the RLD and the Pierrel products are insignificant and therefore no safety or efficacy issues exist.

The biowaiver was granted as of May 19, 2009.

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #6.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #6

If “YES”, list the listed drug(s) identified by name and answer question #5(c).

Articaine Hydrochloride 4% with Epinephrine (Septocaine®)

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If “NO,” proceed to question #11.

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Septocaine®	NDA 20-971	Y
	NDA 22-010	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES NO

If “NO”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

9. Were any of the listed drug(s) relied upon for this application:

- a. Approved in a 505(b)(2) application?

YES NO

If “YES”, please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: Septocaine ® Injection

- b. Approved by the DESI process?

YES NO

If “YES”, please list which drug(s).

Name of drug(s) approved via the DESI process:

- c. Described in a monograph?

YES NO

If “YES”, please list which drug(s).

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d.1.
If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

-The changes include an (b) (4) use of hydrochloric acid as a pH adjuster which results in a higher pH over the RLD and the applicant proposes a larger filling volume.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If “YES” and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If “NO”, proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): **There are no pharmaceutical alternatives for the applicants product.**

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): there are no unexpired patents for this product

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
- Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

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

/s/

AYANNA S AUGUSTUS
10/01/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022466 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: articaïne hydrochloride and epinephrine 1:100,000 and 1:200,000 Dosage Form: injection		Applicant: Pierrel S.p.A. Agent for Applicant (if applicable): Steven Pikulin, TechReg Services, Inc.
RPM: Ayanna Augustus, Ph.D.		Division: Division Anesthesia, Analgesia, and Rheumatology Products
<p>NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>20-971, Septocaine® 22-010, Septocaine®</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>-pH is 3.6 whereas the RLD pH is (b) (4) -Sodium chloride content 1.6 mg/mL, 1.0 mg/mL for RLD -Fill volume is 1.8 mL, 1.7 for RLD -Proposed shelf life is 24 months, 18 months for the RLD -proposed storage (b) (4) for RLD</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		September 25, 2009
❖ Actions		

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<ul style="list-style-type: none"> Proposed action 	<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input checked="" type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ 	<input type="checkbox"/> Received

❖ Application Characteristics ²		
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 4 S/6040100/local anesthetic <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____		
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: <u>Product does not trigger PREA</u>		
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)		<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)		<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)		
• Office of Executive Programs (OEP) liaison has been notified of action		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated		<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire March 30, 2009
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Complete Response, September 25, 2009
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	9/25/09
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	6/22/09
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	11/25/09
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/26/09

<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	
❖ Proprietary Name <ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 8/24/09 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 9/15/09 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews: SEALD 8/20/09; PMHT 7/17/09; CMC 9/23/09
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	March 16, 2009
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	12/10/08, 12/11/08, 2/3/09, 3/19/09, 3/24/09, 4/22/09, 5/21/09, 7/2/09, 7/8/09, 7/24/09, 7/27/09, 7/28/09, 8/6/09
❖ Internal memoranda, telecons, etc.	5/29/09
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date of mtg; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/26/09

<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg June 11, 2008
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/25/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/22/09
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	9/22/09
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	CDTL memo, 9/22/09
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	No clinical studies conducted
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo (<i>indicate date</i>) Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 7, and September 18, 2009
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/26/09

Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 7, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None July 31, 2009
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None July 31, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 2, and 24, 2009
• Product quality review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 14, and September 24, 2009
• ONDQA Biopharmaceutics review (<i>indicate date for each review</i>)	May 19, 2009
• BLAs only: Facility information review(s) (<i>indicate dates</i>)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (<i>indicate date of each review</i>)	August 7, September 18, 2009 <input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	August 14, 2009
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	

<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	<p>Date completed: August 31, 2009</p> <input type="checkbox"/> Acceptable <input checked="" type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	<p>Date completed:</p> <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <p>Date completed:</p> <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

AYANNA S AUGUSTUS
09/25/2009

MEMO TO FILE

To: NDA 22-466
From: Elsbeth Chikhale, Ph.D. – CMC reviewer, ONDQA, DPA I, Branch II
Through: Ali Al-Hakim, Ph.D. – Branch Chief, ONDQA, DPA I, Branch II
Date: September 24, 2009
Subject: Change in Microbiology Recommendation

On August 7, 2009, the application was recommended for approval from microbiology quality standpoint (see review #1 by Steven Fong, Ph.D. dated August 7, 2009). However, on September 18, 2009, a memorandum was filed by the Microbiology Reviewer (see review #2 by Steven Fong, Ph.D. dated September 18, 2009) which concluded that, due to deficiencies related to microbiology in the inspection report, the microbiology recommendation has been revised from approval (review # 1) to withheld (review # 2). The microbiology reviewer requests that the sponsor submits the following information:

- 1) A detailed description of the procedure used to (b) (4) the (b) (4)
- 2) Validation studies demonstrating that the cap and plunger (b) (4) procedure is effective.
- 3) Validation studies for the (b) (4) (b) (4)
- 4) The SOP or a description of the SOP for (b) (4) S. (b) (4) validation that includes a growth promotion test and spore count for (b) (4)
- 5) Validation studies for (b) (4). If validation is conducted with glass cartridges of a different size (b) (4) include a justification for why the results with the alternate cartridges are applicable to the 1.8 mL cartridges.
- 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.

Therefore, from CMC standpoint, the application remains non-approvable due to the following issues:

- Microbiology deficiencies as indicated above.
- Not acceptable recommendation from the office of compliance.

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/

ELSBETH G CHIKHALE
09/24/2009

ALI H AL HAKIM
09/24/2009

MEMO TO FILE

To: NDA 22-466

From: Elsbeth Chikhale, Ph.D. – CMC reviewer, ONDQA, DPA I, Branch II

Through: Ali Al-Hakim, Ph.D. – Branch Chief, ONDQA, DPA I, Branch II

Date: September 23, 2009

Subject: Container/carton label comments from CMC

We concur with all comments from DMEPA (see review by Laura Pincock, PharmD, dated 8/14/09).

In addition, we have the follow CMC comments:

On the cartridge and carton label, revise the drug name and strength below the trade/established name to read as follows:

Tradename® (articaine hydrochloride and epinephrine) Injection

Articaine HCl 4% (40 mg/mL) and epinephrine free base 1:200,000 (containing epinephrine bitartrate 0.0009 mg/mL)

or

Articaine HCl 4% (40 mg/mL) and epinephrine free base 1:100,000 (containing epinephrine bitartrate 0.0018 mg/mL)

Add the following statements to the carton labels:

- For Intraoral Submucosal Injection Only
- Any unused portion of a cartridge should be discarded.
- Parental drug products should be inspected visually for particulate matter and discoloration prior to administration.

Edit/change the following statements on the carton labels:

- Store at room temperature; 25 °C, excursions permitted between 15 and 30 °C.

2 pages of Draft Labeling have been withheld in full immediately following this page as B4 CCI/TS

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/s/

ELSBETH G CHIKHALE
09/23/2009

ALI H AL HAKIM
09/23/2009

Augustus, Ayanna

From: Steven Pikulin [spikulin@comcast.net]
Sent: Thursday, August 06, 2009 9:25 AM
To: Augustus, Ayanna
Subject: RE: Responses to CMC microbiology questions and pdf label files
Attachments: 00721198 originally submitted.pdf; 00721192 originally submitted.pdf; 00721194 originally submitted.pdf; 00721196 originally submitted.pdf

Dear Ayanna: attached are the pdf files for the cartridge/carton labels submitted in the original NDA, with the words "Product Name" in lieu of the actual proposed tradename. Thanks, Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Augustus.Ayanna@fda.hhs.gov]
Sent: Thursday, August 06, 2009 8:57 AM
To: Steven Pikulin
Subject: RE: Responses to CMC microbiology questions and pdf label files

Supply the version with the word "tradename." Thanks.

From: Steven Pikulin [mailto:spikulin@comcast.net]
Sent: Thursday, August 06, 2009 8:55 AM
To: Augustus, Ayanna
Subject: RE: Responses to CMC microbiology questions and pdf label files

Dear Ayanna: do you mean a copy of the labels with something like the word "TRADENAME" in place of the actual proposed tradename, or just a blank spot where the tradename now appears? I can provide the former one now; for the latter one (with blank spot), this request would have to go back to Pierrel and would take some time. Please advise. Thanks, Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Augustus.Ayanna@fda.hhs.gov]
Sent: Thursday, August 06, 2009 8:47 AM
To: Steven Pikulin
Subject: RE: Responses to CMC microbiology questions and pdf label files
Importance: High

Hi Steve,

The CMC reviewer need a copy of the carton and cartridge labels with and without the tradename. Please send a pdf copy of the labels without the tradename as soon as possible.

**Thanks,
Ayanna**

From: Steven Pikulin [mailto:spikulin@comcast.net]
Sent: Thursday, August 06, 2009 8:30 AM
To: Augustus, Ayanna
Subject: Responses to CMC microbiology questions and pdf label files

Dear Ayanna,

As discussed, the following documents are attached to this e-mail:

- Responses to the most current (from July 27 e-mail) CMC microbiology questions. I also included updated responses to 2 of the previous (from July 8 e-mail) CMC microbiology questions (questions 8 and 10). Both the new and updated responses are included in the submission sent yesterday.
- The original pdf files received from Pierrel for the most current drafts of the cartridge and carton labeling (also included in June 22 NDA amendment).

Please let me know if there are any questions.

Thanks,
Steve

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/

AYANNA S AUGUSTUS
09/14/2009

Augustus, Ayanna

From: spikulin@comcast.net
Sent: Thursday, July 30, 2009 1:21 AM
To: Augustus, Ayanna
Cc: spikulin
Subject: Re: Articaïne /Information Requests
Attachments: full labeling text in 8 pt double column format sp 7-30-09.doc

Dear Ayanna: The PLR formatted labeling text in a two-column Word format is attached. I also kept the newly added clinical studies section in a track changes highlighting as you previously requested. Thanks, Steve

----- Original Message -----

From: "Ayanna Augustus" <Ayanna.Augustus@fda.hhs.gov>
To: spikulin@comcast.net
Sent: Tuesday, July 28, 2009 7:22:34 PM GMT -05:00 US/Canada Eastern
Subject: RE: Articaïne /Information Requests

Dear Steve,

The highlights section is formatted correctly but I need the rest of the label included in this document. I think the problem may be that you are sending an SPL formatted document that contains the sections as tables rather than as one continuous document in a two column format. Please send the PLR formatted label with out the embedded tables/columns. If possible please send this by 10AM tomorrow so the team can review it.

I've included a link to the FDA website that has a few examples of fictitious labels in the format requirements we are looking for.

Thanks!
Ayanna

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/u>

From: spikulin@comcast.net [mailto:spikulin@comcast.net]
Sent: Tuesday, July 28, 2009 3:35 PM
To: Augustus, Ayanna
Cc: spikulin
Subject: Re: Articaïne /Information Requests

Dear Ayanna,

Attached are Word copies of the revised labeling and the 120 day safety update. I have also attached a copy of the 8 pt Highlights previously submitted on March 14 as we discussed, which has been submitted in this most current amendment and slightly updated to include the proposed tradename, new revision date and is also offset 0.3" to the right so that the text would not be buried under the binder

9/14/2009

spine in the hard copies. If you offset it 0.3" to the left it exactly meets the FDA formatting requirements. I cannot send you the literature references from the 120 day safety update (which are pdf in any event) because they are embedded as part of a bigger pdf file and I cannot deconvolute them now. I do not think you need these, but I am letting you know.

Thanks,
Steve

----- Original Message -----

From: "Ayanna Augustus" <Ayanna.Augustus@fda.hhs.gov>
To: spikulin@comcast.net
Sent: Tuesday, July 28, 2009 1:05:19 PM GMT -05:00 US/Canada Eastern
Subject: RE: Articaïne /Information Requests

Dear Steve,

Thanks for the note, however the review team needs a WORD copy of the label to work on. Please send an e-copy of the revised label. Also, if you have an e-copy of the 120-day safety report, please send that to me as well.

Thanks,
Ayanna

From: spikulin@comcast.net [mailto:spikulin@comcast.net]
Sent: Tuesday, July 28, 2009 1:02 PM
To: Augustus, Ayanna
Cc: spikulin
Subject: Re: Articaïne /Information Requests

Dear Ayanna: the revised label and 120-day safety update were sent by overnight FedEx yesterday, I just did not get a chance to let you know because I had to rush to the airport. I also included samples of the drug product filled with water as previously requested. Please let me know if this submission was not yet received. The additional microbiology information will be sent by August 3. Thanks, Steve

----- Original Message -----

From: "Ayanna Augustus" <Ayanna.Augustus@fda.hhs.gov>
To: "Steven Pikulin" <spikulin@comcast.net>
Sent: Tuesday, July 28, 2009 7:58:31 AM GMT -05:00 US/Canada Eastern
Subject: RE: Articaïne /Information Requests

Dear Steve,

Please send the revised label and 120-day safety update today as we the team needs this information to complete their review of this application. Submit a response to the additional microbiology IR by Monday August 3rd.

Ayanna

From: Steven Pikulin [mailto:spikulin@comcast.net]

Sent: Monday, July 27, 2009 9:50 AM
To: Augustus, Ayanna
Subject: RE: Articaïne /Information Requests

Dear Ayanna,

The revised label and 120 day safety update are being submitted today, and I will send an electronic copy of the files to you as well.

Please note that I am flying to Pierrel later today to be present for the ongoing PAI, and I will return over the weekend. I am forwarding the additional micro questions and these will be discussed/prepared while at Pierrel, but I need some time after I return to finalize/publish the responses. Accordingly, is it OK if I provide an e-mail response to these questions by Monday, August 3 and submit the paper response by Tuesday, August 4?

Thanks,
Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Ayanna.Augustus@fda.hhs.gov]
Sent: Monday, July 27, 2009 9:20 AM
To: Steven Pikulin
Subject: Articaïne /Information Requests
Importance: High

Dear Steve,

The microbiology review has the following information request:

1. Provide a detailed description of the endotoxin testing protocol, and studies conducted in support of that protocol. The studies should include the results of product inhibition/enhancement and maximum valid dilution assays.
- 2) Provide a detailed description of the sterility testing protocol, and studies conducted in support of that protocol. The studies should include the results of product bacteriostasis and fungistasis assays, and the procedures employed to compensate for product assay interference.
- 3) Provide the procedure for conducting simulated interventions during media fill qualification trials.

Submit a response by Friday July 31st.

In addition, please submit the revised label and a 120-day safety update by COB, today, July 27th.

**Regards,
Ayanna**

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)

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5 pages of Draft Labeling has been withheld in full immediately 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/

AYANNA S AUGUSTUS
09/14/2009

Augustus, Ayanna

From: Fong, Steven
Sent: Friday, July 24, 2009 10:18 AM
To: Augustus, Ayanna
Subject: Additional sponsor questions for NDA 22-466/N-000

Ayanna--

Below in blue are additional (and hopefully final) sponsor questions for NDA 22-466/N-000 (Pierrel (b) (4)). These questions have been approved by the secondary reviewer, Stephen Langille. Please forward to the sponsor and request an "accelerated" response. (NLT August 5th would be appreciated).

Thanks.

Steve

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

Reviewer, New Drug Microbiology Staff
Office of Pharmaceutical Science/CDER
US Food and Drug Administration
10903 New Hampshire Avenue
Bldg 51, Room 4161
Silver Spring, MD 20993-0002
(301) 796-1501

In support of NDA 22-466/N-000, the sponsor is requested to provide:

- 1) A detailed description of the endotoxin testing protocol, and studies conducted in support of that protocol. The studies should include the results of product inhibition/enhancement and maximum valid dilution assays.
- 2) A detailed description of the sterility testing protocol, and studies conducted in support of that protocol. The studies should include the results of product bacteriostasis and fungistasis assays, and the procedures employed to compensate for product assay interference.
- 3) The procedure for conducting simulated interventions during media fill qualification trials.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22466	----- ORIG 1	----- PIERREL S.P.A.	----- ARTICAINE 4% /EPINEPHRINE 1:20000 INJ

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/s/

AYANNA S AUGUSTUS
07/27/2009

QUESTIONS FOR NDA 22-466

In support of NDA 22-466, the sponsor is requested to provide:

- (1) Clarification of the room designated for product fill. The sterility assurance report text (page 5 of 31) states that (b) (4)
[REDACTED]
- (2) A description of the fill line speed and the average number of cartridges to be filled per run.
- (3) A description (size and manufacturer) of the (b) (4)
(b) (4) used for product storage between formulation and cartridge fill.
- (4) The proposed maximum hold time and temperature between product formulation and cartridge fill, and the prefiltration bioburden limit.
- (5) The model type and serial number for the (b) (4)
[REDACTED] that come into direct product contact.
- (6) The minimum and maximum [REDACTED] (b) (4)
[REDACTED]
- (7) The acceptance criteria for (b) (4) used to assess (b) (4) efficacy.
- (8) The validation and production [REDACTED] (b) (4)
[REDACTED]
- (9) A description of environmental monitoring procedures including the alert and actionable levels for each type of monitoring.
- (10) The number of TSB media-filled (b) (4) utilized in the bacterial ingress studies. Include the number of negative controls (assemblies not immersed in *B. diminuta* challenge media) and positive controls (assemblies overtly inoculated with *B. diminuta*).
- (11) A detailed description of the procedure for media fills and the procedures utilized when media fills fail.

- (12) Qualification data for the (b) (4)

- (13) The number of filled cartridges selected for stability testing for the studies presented in Tables 3.2.P.8.3.1-10 through 3.2.P.8.3.1-36.
- (14) The proposed post-approval stability program for evaluating container closure (cartridge/cap/plunger) integrity, sterility, and endotoxin content. Include the proposed testing schedule and test protocol.

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/s/

Ayanna Augustus
7/8/2009 02:39:51 PM
CSO

Augustus, Ayanna

From: Steven Pikulin [spikulin@comcast.net]
Sent: Wednesday, July 08, 2009 4:28 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-466/Micro Information Requests

Dear Ayanna: I have forwarded this request to Pierrel. Pending their input, can we do as requested before, i.e. submit responses by e-mail on Friday, July 17 (or weekend would be better to give a little extra time), followed by paper response on Monday, July 20? Thanks, Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Augustus.Ayanna@fda.hhs.gov]
Sent: Wednesday, July 08, 2009 2:36 PM
To: Steven Pikulin
Subject: NDA 22-466/Micro Information Requests
Importance: High

Hi Steve,

The microbiology reviewer for this NDA has a number of information requests, which are attached as a word document. Please provide a response by Friday, July 17th.

Regards,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)

<<QUESTIONS FOR NDA 22-466.doc>>

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/

AYANNA S AUGUSTUS
09/14/2009

Augustus, Ayanna

From: Steven Pikulin [spikulin@comcast.net]
Sent: Friday, July 03, 2009 8:31 AM
To: Augustus, Ayanna
Subject: RE: CMC Information Request for Articaine

Dear Ayanna,

Just to clarify a couple of points:

- To ensure the July 10 date is met, can an initial response be sent by e-mail (for questions 1-2) followed by hard copy on Monday, July 13? (This might not be necessary, if I get the information soon enough I can combine it with the pH response, but I just want to know my options.)
- For request 3, is there a preference as to how the container closure system is provided, i.e. disassembled cartridge and rubber closures, assembled, with or without drug product?

Thanks,
Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Ayanna.Augustus@fda.hhs.gov]
Sent: Thursday, July 02, 2009 7:58 PM
To: spikulin@comcast.net
Subject: CMC Information Request for Articaine

Hi Steve,

The CMC reviewer has the following information requests:

1. Provide updated stability data if available
2. Provide a table outlining the comparison between the "previous filling line" and the "new filling line".
3. Provide a sample of the container closure system

Please provide the requested information by COB, July 10, 2009.

**Regards,
Ayanna**

*Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
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301-796-3980 (phone)
301-796-9717 (fax)*

Appears This Way On Original



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/

AYANNA S AUGUSTUS
09/14/2009

Augustus, Ayanna

From: Chikhale, Elsbeth G
Sent: Thursday, July 02, 2009 11:16 AM
To: Augustus, Ayanna
Cc: Al Hakim, Ali H
Subject: NDA 22-466

Hi Ayanna,

Can you please send the following IR to the applicant:

1. Provide updated stability data if available
2. Provide a table outlining the comparison between the "previous filling line" and the "new filling line".
3. Provide a sample of the container closure system

Thank you,
Elsbeth

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/s/

Ayanna Augustus
7/2/2009 08:09:07 PM
CSO

REQUEST FOR CONSULTATION

TO (Office/Division): MHT Consult Coordinator; Tammie Brent-Steele, RN MSN

FROM (Name, Office/Division, and Phone Number of Requestor): Division of Anesthesia, Analgesia, and Rheumatology Products/Ayanna Augustus, RPM

DATE 6/5/09	IND NO.	NDA NO. 22-466	TYPE OF DOCUMENT new NDA	DATE OF DOCUMENT 11/24/09
NAME OF DRUG Articaine w/Epinephrine 1:100,00 and 1:200,000		PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG anesthetic	DESIRED COMPLETION DATE 8/18/09

NAME OF FIRM: Pierrel S.p.A.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the maternal and pediatric sections of the labeling for this new NDA. The product labeling is based on the labeling for the RLD, Septocaine (NDA 20-971, NDA 22-010) The labeling is in PLR and is located in the EDR. \\FDSWA150\NONECTD\N22466\N_000\2009-03-14

A hardcopy of the labeling is also attached to this consult. The CDTL for this NDA is Bindi Nikhar. The action date for this application is September 25, 2009. The Wrap-up meeting is scheduled for July 28, 2009. Please email or call Ayanna Augustus if you have any questions (6-3980).

SIGNATURE OF REQUESTOR
Ayanna Augustus

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF

12 pages of Draft Labeling has been withheld in full immediately following this page as B4 CCI/TS

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/s/

Ayanna Augustus
6/5/2009 02:19:00 PM

Augustus, Ayanna

From: Schultheis, Lester
Sent: Friday, May 29, 2009 8:39 AM
To: Augustus, Ayanna; Nikhar, Bindi
Cc: Chikhale, Elsbeth G; Roca, Rigoberto A
Subject: RE: NDA 22-466/Articaine

Folks,

These data satisfy me that the pH of the proposed product is similar enough to the RLD that it will not pose a new clinical risk or change efficacy.

Thanks,

Lex

From: Augustus, Ayanna
Sent: Thursday, May 28, 2009 3:45 PM
To: Nikhar, Bindi; Schultheis, Lester
Cc: Chikhale, Elsbeth G; Roca, Rigoberto A
Subject: FW: NDA 22-466/Articaine
Importance: High

Pierrel has provided a summary of the pH data on fresh RLD batches (This data has also been submitted to the NDA and should arrive by next week). Please weigh in on the information submitted below.

Ayanna

From: Steven Pikulin [mailto:spikulin@comcast.net]
Sent: Thursday, May 28, 2009 7:11 AM
To: Augustus, Ayanna
Subject: RE: NDA 22-466/Articaine

Dear Ayanna,

As per the e-mail below, the pH measurements have been completed and the NDA amendment containing this information is in progress. However, based on more extensive review of RLD documentation after our March 27, 2009 teleconference, this overall issue has taken a somewhat different direction than originally anticipated. Therefore, I am sending you this e-mail to proactively inform the Agency so there are no surprises when this amendment is submitted.

The information provided in response to Comment 4 of the March 14, 2009 amendment to NDA 22-466, and the subsequent March 27, 2009 teleconference to discuss the Septocaine pH results, were based on the conservative premise that the expiration dating period of the RLD is 24 months. However, from more extensive review of FOI-able CMC information from original reviews of the RLD NDAs (numbers 20-971 and 22-010), we have very recently confirmed that the approved expiration dating for the RLD products is not (b) (4), but rather 18 months. This means that any RLD product age calculated from the labeled expiration date is actually 6 months less than stated in the March 14, 2009 amendment, which might render the original concerns from the March 27, 2009 teleconference a moot point.

6/19/2009

Nevertheless, in commitment of our obligation from this teleconference, the pH values from 3 additional Septocaine batches (two 1:100000 and one 1:200000 presentations with regard to epinephrine content), which were the most recently manufactured batches obtainable, have been determined. The ages (using the 18 month expiration dating period) and corresponding pH data for the Septocaine batches for the March 14, 2009 amendment and for those most recently measured in May 2009 are provided in the table below.

Data Source	Septocaine Batch Number	Presentation	pH	Batch Age at time of pH Measurement (months)
March 14, 2009 amendment to NDA 22-466; response to Comment 4	710751	1:100000	3.5	1
	710591	1:200000	3.4	3
Commitment from March 27, 2009 teleconference	0195A	1:100000	3.8	4
	02489	1:100000	3.5	7
	0160A	1:200000	3.6	6

These data clearly indicate that for the RLD, profound pH decreases relative to the formulated pH occur very early in the batch lifetime, which (along with the development data provided in Section 3.2.P.2.2.1, Table 3.2.P.2.2.1-4 of the original NDA) confirm a major decrease in pH (on the order of 1.5 pH units) during (b) (4) of the RLD originally formulated to a target pH of (b) (4).

We believe that these data, along with this explanation, provide closure on this issue. This information will of course be included in complete detail in the upcoming NDA amendment. Please let us know if this constitutes a satisfactory response and if there are any other related comments at this time.

Thanks,
Steve

-----Original Message-----

From: Steven Pikulin [mailto:spikulin@comcast.net]
Sent: Thursday, May 21, 2009 1:33 PM
To: 'Augustus, Ayanna'
Subject: RE: NDA 22-466/Articaine

Dear Ayanna,

As per agreement, pH data have been recently generated for 3 batches of Septocaine (two 1:100000 and one 1:200000 batches w/respect to epinephrine content), which were obtained from a distributor with a request to provide the most recently manufactured batches available. All pH values were at or below 3.8. I still need to perform a little more research regarding the expiration dating period for the RLD to better understand the age of these batches. Once this is done, the results with appropriate discussion will be submitted (I anticipate no later than Monday, June 1, possibly sooner).

Thanks,
Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Augustus.Ayanna@fda.hhs.gov]
Sent: Tuesday, May 19, 2009 11:11 AM
To: Steven Pikulin
Subject: NDA 22-466/Articaine
Importance: High

Hello Steve,

The review team recently held the Mid-cycle review meeting for this NDA. At present we are still awaiting pH data on the fresh RLD samples as discussed during our March 27, 2009 teleconference. Can you provide a timeframe for when the Division will receive this data?

Regards,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)

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/s/

Ayanna Augustus
6/19/2009 03:07:56 PM
CSO

Augustus, Ayanna

From: Steven Pikulin [spikulin@comcast.net]
Sent: Thursday, May 21, 2009 1:26 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-466/Articaine/PT Information Request

Dear Ayanna: this request has been forwarded to Pierrel and I will let you know as soon as I know something regarding response timeframe. I will also be providing feedback to your other recent e-mails regarding the pH study and labeling shortly. Thanks, Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Augustus.Ayanna@fda.hhs.gov]
Sent: Thursday, May 21, 2009 1:02 PM
To: spikulin@comcast.net
Subject: NDA 22-466/Articaine/PT Information Request
Importance: High

Hello Steve,

Please convey to Pierrel the following pharmacology/toxicology information request:

- 1) Based on the information in your submission, there are two potential process impurities (b) (4) that contain structural alerts for mutagenicity listed in your Articaine HCl drug substance that do not have specifications. These impurities are Ph.Eur (b) (4) and Ph.Eur (b) (4). Although you note that these impurities are not observed at the ICH Q3A(R2) identification level, since these impurities contain a structural alert for mutagenicity, they must either be reduced to not more than (b) (4) or adequate safety qualification must be provided. Provide actual levels for these two impurities in the drug substance (certificate of analysis or batch analysis data) and, if present, include a specification for these impurities such that the total daily exposure will not exceed (b) (4).
- 2) In addition, provide data to demonstrate that these two impurities are also not degradants. If they are also drug product degradants, a specification must be established in the drug product such that the total daily exposure will not exceed (b) (4).

Please provide an approximate timeframe for when we might receive responses. In addition to submitting the requested information to the NDA, please send an electronic copy to me.

Regards,
Ayanna

*Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219*

*10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)*

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/s/

Ayanna Augustus
6/29/2009 04:36:12 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-466

Pierrel S.p.A.
c/o TechReg Services, Inc
17 McIntire Drive
Hillsborough, NJ 08844

Attention: Steven Pikulin, Ph.D., RAC
US Agent for Pierrel S.p.A.

Dear Dr. Pikulin,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000; injection; 40 mg/ml; 10 and 5 µg/ml.

We also refer to the teleconference between representatives of your firm and the FDA on March 27, 2009. The purpose of the meeting was to discuss data submitted in an amendment dated March 14, 2009, which provided a response to the Division's request for additional data on the reference listed product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure-Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 27, 2009
TIME: 11:30 AM
APPLICATION: NDA 22-466
DRUG NAME: Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000
TYPE OF MEETING: Teleconference
MEETING CHAIR: Bindi Nikhar, MD, Clinical Team Leader
 Division of Anesthesia, Analgesia and Rheumatology Products
MEETING RECORDER: Ayanna Augustus, PhD, Regulatory Project Manager

FDA Attendees	Title
Rigoberto Roca, MD	Deputy Division Director
Bindi Nikhar, MD	Clinical Team Leader
Lex Schultheis, MD, PhD	Clinical Reviewer
Mitchell Frost, M.D.	Clinical Reviewer
Dan Mellon, PhD	Team Leader, Pharmacology/Toxicology
Charlic Huynh, PhD	Pharmacology/Toxicology Reviewer
Elsbeth Chikhale, PhD	Chemistry, Manufacturing and Controls Reviewer
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead, CMC
Fred Hyman, M.D.	Clinical Reviewer, Division of Dermatology and Dental Products
Ayanna Augustus, PhD	Regulatory Project Manager
Sponsor Attendees	Title
Manfred Schlemminger	Director Regulatory Affairs, Pharmapart
Andrea Singer, PhD	Senior Regulatory Affairs Manager and Medical Writer, Pharmapart
Fulvio Carlotti	Plant Manager, Pierrel
Toni Valente	Regulatory Director, Pierrel
Angelo Colombo	Business Development, Pierrel
Steven Pikulin, PhD, RAC,	TechReg Services Inc

BACKGROUND:

NDA 22-466 for Articaine Hydrochloride 4% Epinephrine 1:100,000 and 1:200,000 injection, manufactured by Pierrel S.p.A., was submitted as a 505(b)(2) application on November 24, 2008. The bases for this application were the reference listed drugs (RLD) Septocaine ® Injection (Articaine Hydrochloride 4% Epinephrine 1:100,000 (NDA 20-971) and 1:200,000 (NDA 22-010). In a letter dated February 3, 2009, the Division communicated potential review issues to the Sponsor and requested additional information on the pH of the RLD. In an amendment dated March 14, 2009, the Sponsor provided pH data for commercially available batches of RLD product, which were approximately nine months old. The Sponsor indicated that the age of the RLD batches tested was calculated from the expiration date noted on the RLD cartons. The Division asked the Sponsor to provide pH data on one-, three-, and six-month old RLD batches. The Sponsor indicated that additional pH measurements for the RLD were not collected at the requested time points. Therefore, the Division requested a teleconference with the Sponsor to discuss what additional data would need to be provided to adequately assess the Sponsors' claim that their product is comparable to the RLD.

DISCUSSION

Following introductions, the Sponsor indicated that their NDA contained stability data (Sections 3.2.P.2.2.1) that demonstrated that when the drug product, articaine, was formulated to an initial target pH of the RLD, and subjected to processing conditions that mimicked (b) (4). The Sponsor believed that the labeled pH of (b) (4) for the RLD reflects the pH of the product before (b) (4). The Sponsor indicated that data in their NDA support their conclusion that the rapid and significant drop in pH of the RLD was due to the affects of (b) (4). The Sponsor also mentioned that the pH of the drug product formulation remained relatively constant and did not drop more than 0.3-0.4 units over the 24-month testing period.

The Division informed the Sponsor that data from the Septocaine NDAs could not be used to evaluate and review their application for Articaine unless the Sponsor obtained a right of reference to the data. The Division requested that the Sponsor provide the pH measurements for batches of the RLD from time of release until the pH of the RLD drops to levels observed for their product. The Sponsor should also provide additional justification to support their conclusion that the pH results of the experimental formulated drug product (b) (4) (b) (4) reflect the pH of the RLD product after (b) (4) and at the time of release.

To support the claim that their product is similar to the RLD, the Sponsor suggested procuring additional RLD batches from different lots and with different release dates, measuring the pH of each sample and submitting these data to the NDA. The Division indicated that variability in the storage conditions for RLD samples collected from different lots and with different manufacture release dates may affect interpretation of these data. The Division emphasized that it would be preferable to procure the freshest batches of the RLD, maintain them under controlled conditions (25°C/60% humidity) in order to mimic pre-specified storage conditions of the RLD, periodically measure the pH of the RLD samples and identify the elapsed time required for the RLD pH to

approximate the pH of the Sponsor's product. The Sponsor questioned the need to provide additional pH data for the RLD samples if they were able to demonstrate a pH of approximately 3.5 for RLD batches that are one or two months old. The Division agreed that additional data would not be necessary, but would expand the time-pH profile for the RLD. The Sponsor agreed to try to obtain the freshest sample of the RLD product, maintain the RLD batches at a constant temp and humidity previously mentioned and measure the pH of the RLD batches over a period of time until the pH levels of the RLD batches were comparable to the pH of their drug product. The Sponsor indicated that they will also measure the pH of the RLD from different lots and at different manufacturer release dates and submit these data to the NDA as a separate submission.

ACTION ITEMS:

1. The Sponsor will procure as many batches, but no fewer than three batches of the RLD manufactured as recently as possible. The Sponsor will store all batches at 25°C and 60% relative humidity in an attempt to mimic pre-specified storage conditions for the RLD. The Sponsor will submit pH measurements for the freshest batches of RLD.
2. The Sponsor will provide a time-pH profile for all RLD batches if the Sponsor observes a pH of 3.8 or greater for any of the batches tested. The pH levels will be obtained over regular intervals until the imprinted expiration date or no further changes in the pH are observed.
3. The Sponsor will provide further discussion of the original NDA study described in Section 3.2.P.2.2.1, Table 3.2.P.2.1-4 of NDA 22-466.
4. The Sponsor will provide a timeframe for submission of these data once US marketed RLD batches have been obtained.

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/s/

Ayanna Augustus
4/22/2009 08:22:16 AM

Augustus, Ayanna

From: Steven Pikulin [spikulin@comcast.net]
Sent: Tuesday, March 24, 2009 2:15 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-466/Articaine/ Request for Tcon

Dear Ayanna: I will send this to Pierrel asap. I am available at 11:30 am but I cannot speak for Pierrel. It would also be helpful for them to have a brief agenda or some idea of the Agency questions. Would it be possible to provide this? Thanks, Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Ayanna.Augustus@fda.hhs.gov]
Sent: Tuesday, March 24, 2009 1:45 PM
To: Steven Pikulin
Subject: NDA 22-466/Articaine/ Request for Tcon
Importance: High

Hello Steve,

The review team would like to arrange a teleconference with the Sponsor to discuss a few clinical concerns. Please indicate if you and the sponsor are available on Friday, March 27th at 11:30 AM. If so, please provide a call-in number for this tcon.

Regards,

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22, Rm 3219
301-796-3980 (phone)
301-796-9717 (fax)

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/

AYANNA S AUGUSTUS
09/14/2009

Augustus, Ayanna

From: Steven Pikulin [spikulin@comcast.net]
Sent: Thursday, March 19, 2009 11:40 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-466/Articaine/ Information Request
Attachments: final response to comment 4.pdf

Dear Ayanna,

Pursuant to our brief phone discussion earlier today, I have attached a pdf version of the submitted response in question. This should be the exact same text provided in the March 14 submission, but if for some reason it is not, please let me know.

Just for clarity, there are a couple of minor typos on this page. Table 3c-1 should be called Table 4-1 according to the convention used in this submission; and at the bottom of this table, the last footnote (included within the table border) should have two asterisks instead of one. These are minor, but this last typo regarding the missing asterisk might have some bearing on the understanding of the response, so I am bringing this to your attention.

From the attached response, you will notice that there are two places where there is information relevant to the reviewer request from the e-mail below:

- In the text immediately above the table, the last sentence states: "The Septocaine batches were obtained from the US market and the time of testing was calculated based on the imprinted expiry date and an assumed expiration dating period of 24 months."
- The asterisked footnotes at the bottom of the table state: "The cited result assumes a 24 month expiration dating period, corresponding to testing 7 months (or 9 months) after manufacture."

So to make a long story short, the explanation I gave you earlier today is correct, i.e. Pierrel obtained the Septocaine batches from the US market, looked at the imprinted expiration dates on the cartons and assumed a 24 month expiry period which then gives the manufacturing dates for these batches. Using this logic, the dates on which the pH measurements for these batches were made by Pierrel correspond to 7 months and 9 months after manufacture for the 1:100000 and 1:200000 products, respectively.

To my knowledge (I am 99% sure, but still checking on this), no other pH measurements were taken at any other times for these Septocaine batches, since the point was proven that the initial pH (nominally (b) (4) based on the Septocaine package insert) decreased to the same level as the Pierrel products in a relatively short time. These results are also consistent with the experiment performed by Pierrel described in Section 3.2.P.2.2.1 of the original NDA (p. 2 of 5, middle of page), with the results summarized in Table 3.2.P.2.2.1-4 of the original NDA.

Hopefully this is all clear. Please let me know if we need to discuss further.

Thanks,
Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Augustus.Ayanna@fda.hhs.gov]
Sent: Thursday, March 19, 2009 12:47 PM
To: spikulin@comcast.net
Subject: NDA 22-466/Articaine/ Information Request
Importance: High

Hello Steve,

The clinical reviewer for this application has the following information request for the sponsor:

1) Table 3c-1 presents pH data for other approved articaine products, including the reference listed product, Septocaine. However the table only provides data on the pH of Septocaine 9 months after manufacturing. Provide the pH information for Septocaine at 0, 3, and 6 months post manufacturing.

Provide this information by close of business Friday, March 20th.

Regards,

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Bldg. 22, Rm 3219
301-796-3980 (phone)
301-796-9717 (fax)

FDA Comment:

- 4. Provide detailed data for your comparison of pH of your product with approved articaine dental products (e.g. on stability). Include the latency between the date of manufacture and the date of testing.**

Pierrel Response:

The articaine data from the original NDA (Section 3.2.P.2.2.1, Table 3.2.P.2.2.1-3) has been expanded in Table 3c-1 below to include the available stability data generated at Pierrel; further information for other listings in Table 3.2.P.2.2.1-3 is currently unavailable. The Pierrel articaine products which are the subject of this NDA are excluded from the table below since stability data are already provided in Section 3.2.P.8 of the original NDA. For clarification, the Citocartin and Cartidont products are also manufactured by Pierrel for Molteni and Curaden, respectively, using processes and quality criteria similar to but not identical with the NDA product, and the stability data for these batches were generated immediately after manufacturing/release were completed. The Septocaine batches were obtained from the US market and the time of testing was calculated based on the imprinted expiry date and an assumed expiration dating period of 24 months.

Table 3c-1. Overview of Available Stability Data for other Articaine Products in Table 3.2.P.2.2.1-3 of the Original NDA							
Articaine Drug Product	Storage Time at 25C/60% RH (months)						
	0	3	6	9	12	18	24
Citocartin (Molteni), 1:100000 epinephrine	3.9	4.0	3.7	3.8	3.6	3.5	3.4
Citocartin (Molteni), 1:200000 epinephrine	3.7	4.1	3.6	3.9	3.6	3.5	3.4
Cartidont (Curaden), 1:100000 epinephrine	3.6	3.9	3.8	3.5	3.5	3.4	3.6
Cartidont (Curaden), 1:200000 epinephrine	3.7	4.1	4.0	4.0	3.6	3.5	3.4
Septocaine (Septodont, batch number 710751, expires July 2009), 1:100000 epinephrine*	----	----	----	3.5	----	----	----
Septocaine (Septodont, batch number 710591, expires May 2009), 1:200000 epinephrine**	----	----	----	3.4	----	----	----
* The cited result assumes a (b) (4) expiration dating period, corresponding to testing 7 months after manufacture. * The cited result assumes a (b) (4) expiration dating period, corresponding to testing 9 months after manufacture.							

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/

AYANNA S AUGUSTUS
09/14/2009

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-466 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Articiane Hydrochloride 4%, with Epinephrine 1:100,000 and 1:200,000 Dosage Form: injection Strengths: 40 mg/ml; 10 and 5 mg/ml epinephrine		
Applicant: Pierrel S.p.A. Agent for Applicant (if applicable): Steven Pikulin, Ph.D., TechReg Services, Inc		
Date of Application: 11/24/08 Date of Receipt: 11/25/08 Date clock started after UN:		
PDUFA Goal Date: 9/25/09		Action Goal Date (if different):
Filing Date: 2/7/09 Date of Filing Meeting: 1/15/09		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3 (new formulation), 4 (new combination)		
Proposed Indication(s): local, infiltrative or conductive anesthesia in both simple and complex dental (b) (4) procedures		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Refer to Appendix A for further information.		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify	

Other:	clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): PIND 101,935	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i> If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i> If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><i>the Electronic Orange Book at:</i> http://www.fda.gov/cder/ob/default.htm</p>		
<p>If yes, please list below:</p>		
Application No.	Drug Name	Exclusivity Code
22-010	Articaine Hydrochloride 4% with Epinephrine 1:200,000	NP
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>		
<p>Format and Content</p>		
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>		
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If electronic submission, does it follow the eCTD guidance? http://www.fda.gov/cder/guidance/7087rev.pdf</p>		<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If not, explain (e.g., waiver granted):</p>		

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments: requested waiver for bioequivalence studies</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p>PREA</p>	
<p>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>Comments: pediatric studies using the RLD are sited</p>	
<p>BPCA (NDAs/NDA efficacy supplements only):</p>	

<p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
Prescription Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<p><input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)</p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Package insert (PI) submitted in PLR format?</p> <p>If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>REMS consulted to OSE/DRISK?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): June 11, 2008 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING**DATE:** 1/15/09**NDA/BLA #:** 22-466**PROPRIETARY/ESTABLISHED NAMES:** Articiane Hydrochloride 4%, with Epinephrine 1:100,000 and 1:200,000**APPLICANT:** Pierrel S.p.A.**BACKGROUND:**

Molecular entity is already approved and this NDA is for a formulation that has increased sodium chloride concentration and a higher pH and filling volume. The product is sold in Italy. RLD is Septocaine with Epinephrine. PreNDA meeting was held June 11, 2008

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ayanna Augustus	y
	CPMS/TL:	Parinda Jani	n
Cross-Discipline Team Leader (CDTL)	Bindi Nikhar		y
Clinical	Reviewer:	Lex Schultheis	y
	TL:	Bindi Nikhar	y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OSE	Reviewer:	Joann Lee	y
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sirkanth Nallani	y
	TL:	Suresh Doddapanai	y
Biostatistics	Reviewer:	N/A	
	TL:	Dionne Price	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carlic Huynh	y
	TL:	Dan Mellon	y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Elsbeth Chikhale	y
	TL:	Danae Christodoulou	y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:	Steven Fong	y
	TL:	Jim McVey	n
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Martin Pollock (OSE), Art Simone (DAARP), Chris Wheeler (OSE), Ali Al-Hakim (ONDQA), Laura Pincock (OSE), Kim Compton (DAARP), Eva Lee (OSE), Jay Chang (DAARP), Allison Meyer (DAARP), Mitch Frost (DAARP)

505(b)(2) filing issues? If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain: Five referenced articles are either in German or Slovak.	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? If no, explain: clinical studies were not conducted 	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason: 505(b)(2) submission</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments: Two establishment ready and one establishment will be ready for inspections by the end of the second quarter in 2009.</p> <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Bob A. Rappaport, M.D.</p> <p>GRMP Timeline Milestones: Mid-cycle meeting 4/29/09; Wrap-up meeting 7/21/09</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<input checked="" type="checkbox"/>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<input type="checkbox"/>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.</p>
<input type="checkbox"/>	<p>If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<input type="checkbox"/>	<p>If BLA or priority review NDA, send 60-day letter.</p>
<input checked="" type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>
<input type="checkbox"/>	<p>Other</p>

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

Ayanna Augustus
3/16/2009 03:18:20 PM
CSO



FILING COMMUNICATION

NDA 22-466

Pierrel S.p.A.
c/o TechReg Services, Inc
17 McIntire Drive
Hillsborough, NJ 08844

Attention: Steven Pikulin, Ph.D., RAC
US Agent for Pierrel S.p.A.

Please refer to your new drug application (NDA) dated November 24, 2008, received November 25, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Articaine Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000; injection; 40 mg/ml; 10 and 5 ug/ml.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 14, 2009

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 25, 2009.

During our filing review of your application, we identified the following potential review issues:

1. Revise the package insert labeling to address the following:
 - a. Edit the Highlights section such that it is limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5" x 11 paper, single spaced, 8 point type with ½ inch margins on all sides, in a two-column format).

- b. Add bullet point to the subheadings in section 2.2
- c. Include the following statement preceding presentation of adverse reactions from clinical trials: “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

(b) (4)

[Redacted text block]

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

- a. [Redacted text] (b) (4)
These stoppers should be evaluated.
- b. [Redacted text] (b) (4)
- c. If the studies discussed above do not resolve the degradation question, evaluate an additional [Redacted text] (b) (4) after [Redacted text] (b) (4).

4. Provide detailed data for your comparison of pH of your product with approved articone dental products (e.g., on stability). Include the latency between the date of manufacture and the date of testing.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a full waiver of pediatric studies for this application for all pediatric patients.

If you have any questions, call Ayanna Augustus, Regulatory Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
2/3/2009 04:21:05 PM

MEMORANDUM

From: Danae D. Christodoulou, Ph.D., ONDQA Branch II
Through: Ali Al-Hakim, Ph. D., Branch Chief, ONDQA Branch II;
To: NDA 22-466
Subject: Addendum to Initial Quality Assessment
Date: 2/2/09

Correction, IQA p. 1: The proposed route of administration for articaine HCl 4% with epinephrine bitartrate 1:100,000 and 1:200,000 w/v is:
“Local, infiltrative or conductive anesthesia in dental (b) (4)
procedures”, i.e., by submucosal infiltration or nerve block; (b) (4)
(b) (4)

Danae D. Christodoulou, Ph.D. 2/2/09

Pharmaceutical Assessment Lead, ONDQA

Ali Al-Hakim, Ph.D. 2/2/09

Branch II Chief, ONDQA

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/s/

Danae Christodoulou
2/2/2009 11:11:18 AM
CHEMIST
Addendum to Initial Quality Assessment

Ali Al-Hakim
2/2/2009 02:39:30 PM
CHEMIST

REQUEST FOR CONSULTATION

TO (Office/Division): **Patrick Marroum CDER/OPS/ONDQA**

FROM (Name, Office/Division, and Phone Number of Requestor): **Don Henry
Project Manager, ONDQA, 301-796-4227 on behalf of
Danae Christodoulou/Elsbeth Chikhale**

DATE
January 14, 2009

IND NO.

NDA NO.
22-466

TYPE OF DOCUMENT
NDA submission

DATE OF DOCUMENT
November 24 2008

NAME OF DRUG
Articaine/Epinephrine

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
Anesthetics

DESIRED COMPLETION DATE
May 1, 2009

NAME OF FIRM: **Pierrel**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input checked="" type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The applicant has requested a waiver of the bioequivalency study. The application (Section 1.12.15) provides the justification for the request. This section will be delivered to Biopharmaceutics for review.

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Ali Al-Hakim
1/15/2009 03:35:28 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **Sylvia Gantt/Jim McVey New Drug Microbiology Staff OC/OO/CDER/OPS/NDMS**

FROM (Name, Office/Division, and Phone Number of Requestor): **Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of Danae Christodoulou/Elsbeth Chikhale**

DATE
January 13, 2009

IND NO.

NDA NO.
22-466

TYPE OF DOCUMENT
NDA submission

DATE OF DOCUMENT
November 24 2008

NAME OF DRUG
Articaine/Epinephrine

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
Anesthetics

DESIRED COMPLETION DATE
May 1, 2009

NAME OF FIRM: **Pierrel**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology consultation is requested to review the manufacturing process and specifications for this product.

SIGNATURE OF REQUESTOR
{See appended electronic signature page }

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Ali Al-Hakim
1/13/2009 09:41:14 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **OSE/DMEPA/Chris Wheeler, RPM**

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Anesthesia, Analgesia, and Rheumatology Products/Ayanna Augustus, RPM**

DATE
12.12.08

IND NO.

NDA NO.
22-466

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
11.25.08

NAME OF DRUG
Articaine

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
anesthetic

DESIRED COMPLETION DATE
7.1.09

NAME OF FIRM: **Pierrel S.p.A.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the labels for promotional potential. This is PLR. The carton and container labels have been scanned and are attached to this consult. The package insert label is located electronically in the EDR. A hardcopy of the carton and container labels submitted with the application will also be provided.
\\FDSWA150\NONECTD\N22466\N_000\2008-11-24

SIGNATURE OF REQUESTOR
Ayanna Augustus

METHOD OF DELIVERY (Check one)
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PRINTED NAME AND SIGNATURE OF DELIVERER

1.14 Labeling

1.14.1 Draft Labeling

1.14.1.1 Draft Carton and Container Labels

The draft mock labeling for Articaine Hydrochloride 4% with Epinephrine 1:100000 Injection and Articaine Hydrochloride 4% with Epinephrine 1:200000 Injection consists of the following:

- Draft package insert, prepared in Structured Product Labeling-Physician Label Rule (SPL-PLR) format pursuant to 21 CFR §§201.56 and 201.57, provided as a CD attached to the archived copy of Module 1 (containing the body of the package insert in XML format, chemical structures in separate graphic files and a Microsoft Word reproduction of the draft labeling. The Microsoft Word reproduction is also provided in Sections 1.14.1.2 and 1.14.1.3 of this submission.
- Draft cartridge label artwork, provided in this section.
- Draft carton label artwork, provided in this section.

The following additional points are noted regarding the draft labeling:

- A proposed proprietary name has not yet been selected, and the term "Product name" is currently used as a placeholder in the draft cartridge/carton labeling
- It is noted that the NDC number (to be assigned) is improperly located on the draft carton label and will be repositioned to the upper one third of the label panel.

3 pages of Draft Labeling has been withheld in full immediately following this page as B4 CCI/TS

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/s/

Ayanna Augustus
12/31/2008 01:16:33 PM



NDA 22-466

NDA ACKNOWLEDGMENT

Pierrel S.p.A.
c/o TechReg Services, Inc
17 McIntire Drive
Hillsborough, NJ 08844

Attention: Steven Pikulin, Ph.D. RAC
US Agent for Pierrel S.p.A.

Dear Dr. Pikulini:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Articaïne Hydrochloride 4% with Epinephrine 1:100,000 and 1:200,000; injection; 40 mg/ml; 10 and 5 ug/ml

Date of Application: November 24, 2008

Date of Receipt: November 25, 2008

Our Reference Number: NDA 22-466

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 24, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Drugs
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Ayanna Augustus
12/11/2008 08:17:08 AM

Augustus, Ayanna

From: Steven Pikulin [spikulin@comcast.net]
Sent: Thursday, December 11, 2008 1:09 AM
To: Augustus, Ayanna
Subject: RE: NDA 22-466
Follow Up Flag: Follow up
Flag Status: Blue

Dear Ayanna,

There is currently no tradename for the product. It is anticipated that a tradename will be proposed during the NDA review period and an amendment to the NDA will be submitted with the requested information.

It is no problem to provide the CMC section on a CD and I will send it along with the CMC microbiology copy and the Module 1 desk copy no later than Monday.

Thanks,
Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Augustus.Ayanna@fda.hhs.gov]
Sent: Wednesday, December 10, 2008 3:33 PM
To: spikulin@comcast.net
Subject: RE: NDA 22-466

Hello Steve,

If there is a tradename for this product, please submit an amendment to the NDA with the following information.

Indication
Dosage form
Strength
Usual Dose
Dosing Frequency
Prescribing Population
Packaging Information (if injectable)
Route of Administration
Any unique product characteristics for the drug
Major adverse events that may have been identified
Working model of drug delivery device (if applicable)
All labeling: professional and patient (if any)

In addition, the CMC reviewer would like to know if you can provide an electronic copy of the CMC section of this NDA (i.e. CD).

Regards,
Ayanna

From: spikulin@comcast.net [mailto:spikulin@comcast.net]
Sent: Wednesday, December 10, 2008 10:31 AM
To: Augustus, Ayanna
Subject: Re: NDA 22-466

Got it. Thanks, Steve

----- Original Message -----

From: "Ayanna Augustus" <Ayanna.Augustus@fda.hhs.gov>
To: spikulin@comcast.net
Sent: Wednesday, December 10, 2008 9:30:15 AM GMT -05:00 US/Canada Eastern
Subject: RE: NDA 22-466

Hello Steve,
Please send all the the relevant volumes/modules needed for the CMC microbiology reviewer. In addition, I will need a desk copy of module 1.

Thanks

From: spikulin@comcast.net [mailto:spikulin@comcast.net]
Sent: Wednesday, December 10, 2008 9:21 AM
To: Augustus, Ayanna
Cc: spikulin
Subject: Re: NDA 22-466

Dear Ayanna: just to be clear, is the Module 1 copy for the CMC microbiology reviewer as well (so it can be labeled accordingly), or is it just a general desk copy? Thanks, Steve

----- Original Message -----

From: "Ayanna Augustus" <Ayanna.Augustus@fda.hhs.gov>
To: "Steven Pikulin" <spikulin@comcast.net>
Sent: Monday, December 8, 2008 3:09:47 PM GMT -05:00 US/Canada Eastern
Subject: RE: NDA 22-466

Hello Steve,

Thanks for the quick response. Please send a copy of Module 1 as well as the CMC-microbiology modules (red binder is sufficient) by Tuesday, December 16th.

Please email me if you have any additional questions.

Regards,
Ayanna

From: Steven Pikulin [mailto:spikulin@comcast.net]
Sent: Saturday, December 06, 2008 4:58 PM
To: Augustus, Ayanna

Cc: spikulin@comcast.net
Subject: RE: NDA 22-466

Dear Ayanna,

Thanks for your e-mail and I look forward to working with you on this NDA. I have a couple of requests/questions:

- When you say a “desk copy of Volume 1”, I assume you mean a desk copy of Module 1, correct?
- This coming week (the week of Dec. 8) I will be traveling outside of the US. In my absence I have somebody helping to prepare the requested desk copies for the CMC-microbiology reviewer, but I need to look it over before it goes out to make sure it has been properly copied and assembled. Would it be OK if you receive this no later than Tuesday, Dec. 16 (i.e. I will send it by overnight mail to you no later than Monday, Dec. 15)? I might be able to do it a little sooner but I do not want to commit to a date that I am not certain I can meet.
- I am currently out of the NDA binders for microbiology (they are currently back-ordered). Is there any problem if I use, say, the CMC (red) binders, or just any blank binder, with appropriate labeling on the cover to indicate it is a review copy for micro?

I am sorry to be a pest but things are a bit hectic right now and it would be very helpful if you could accommodate these requests.

Best Regards,
Steve

-----Original Message-----

From: Augustus, Ayanna [mailto:Ayanna.Augustus@fda.hhs.gov]
Sent: Friday, December 05, 2008 10:35 AM
To: spikulin@comcast.net
Subject: NDA 22-466

Dear Dr. Pikulin,

My name is Ayanna Augustus and I will be the Project Manager for your new drug application. You should receive a letter acknowledging your application by next week.

Please send a deck copy of the CMC volumes for the CMC-Microbiology reviewer and a desk copy of volume 1. You can mail these volumes to me at the address below.

Regards,

Ayanna Augustus, Ph.D.

Regulatory Project Manager

Division of Anesthesia, Analgesia,

and Rheumatology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Ave

Bldg. 22, Rm 3219

301-796-3980 (phone)

301-796-9717 (fax)

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

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

/s/

AYANNA S AUGUSTUS
09/14/2009