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APPLICATION NUMBER:

022569Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

17-MAR-2010

NDA 22-569/N-000.

Drug Product Name
Proprietary: Lazanda
Non-proprietary: Fentanyl Nasal Spray

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
09-MAR-2011	09-MAR-2011	N/A	N/A
21-FEB-2011	22-FEB-2011	N/A	N/A
30-SEP-2010	30-SEP-2010	N/A	05-JAN-2011

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
30-AUG-2009	1	12-MAY-2010

Applicant/Sponsor

Name: Archimedes Development, Limited
Address: Nottingham Science and Technology Park
University Boulevard
Nottingham NG7 2TN
United Kingdom
Representative: Ann Tunstall
SciLucent, LLC
Telephone: 703-435-0033 X224

Name of Reviewer: Steven Fong, Ph.D.

Conclusion: CMC-Microbiology recommends APPROVE.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: NDA 505(b)(2).

2. SUBMISSION PROVIDES FOR: New drug product: [redacted] (b) (4) nasal spray [redacted] (b) (4)

3. MANUFACTURING SITE: [redacted] (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: [redacted] (b) (4) multi-dose nasal spray containing 1.57 mg/mL or 6.28 mg/mL fentanyl citrate salt.

5. METHOD(S) OF STERILIZATION: N/A. [redacted] (b) (4).

6. PHARMACOLOGICAL CATEGORY: Narcotic.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:

1) The subject NDA was initially received 30-AUG-2009 and a Microbiology Quality Review (Review 1) was submitted 12-MAY-2010. The latter cited deficiencies pertaining to detection of *Burkholderia cepacia* in the bulk product and the raw materials used for formulation (see Page 6 of current review). These deficiencies were conveyed to the Applicant in a 08-MAR-2010 IR letter, and on 03-JUN-2010 the Applicant provided an Amendment Response (Supporting Document 20). This Amendment was not reviewed in the first review cycle because it was received too late for consideration. The deficiencies cited in Review 1 were included in a CR letter issued 30-JUN-2010.

2) On 09-AUG-2010 the Applicant provided a meeting package (Supporting Document 22) for a face-to-face meeting held 24-AUG-2010. The package included two questions (4 and 5) pertaining to microbiology quality, responses for which were included in preliminary responses submitted 23-AUG-2010. The questions and Agency responses were as follows:

Applicant Question 4: Archimedes has submitted an assay for detecting Burkholderia cepacia in the drug product in NDA Amendment 19 (submitted on 03-JUN-2010). Archimedes has also included a specification for the absence of Burkholderia cepacia in the drug product. The data included in Amendment 19 is outlined in Appendix 3 and will be resubmitted with the response to the deficiencies identified in the Complete Response Letter. Does FDA agree that this is appropriate?

Agency Response: The revised specification stating absence of B. cepacia as well as P. aeruginosa and S. aureus is appropriate and acceptable. The proposed B. cepacia test method (Submission Section 3.2.P.5.2.8) in which the bacterium is enriched in tryptic soy broth (TSB) prior to isolation and detection on OFPBL agar plates is also appropriate and acceptable. However, TSB may not represent an optimal enrichment medium for strains derived from nutrient-poor environments (see Carson et al., Appl. Micro. 25(3):476-483; 1973), and you are encouraged to consider alternative media.

Applicant Question 5. Archimedes has submitted a commitment to test for Burkholderia cepacia contamination in the Purified Water, USP, (b) (4) (b) (4) in NDA Amendment 19 (submitted 03-JUN-2010). The commitment will be resubmitted with the response to the deficiencies identified in the Complete Response Letter. Does the FDA agree that this is appropriate?

Agency Response: The commitment to test for B. cepacia in the Purified Water USP (b) (4)

3) The NDA was resubmitted electronically in CTD format on 30-SEP-2010 (Supporting Document 24). Attachment 1 of the resubmission included responses to two microbiology quality deficiencies cited in the 30-JUN-2010 CR letter. These responses encompassed those presented in the 03-JUN-2010 Amendment and the 09-AUG-2010 meeting package. The current review considers the responses in the 30-SEP-2010 resubmission.

4) On 07-FEB-2011 an information request was submitted to the Applicant requesting validation procedures and data summaries for the *B. cepacia* detection assay, the source and identity of the *B. cepacia* strain used for validation, and the temperature of the Purified Water USP (b) (4) (b) (4). An Amendment response (Supporting Document 34) was received 22-FEB-2011.

5) On 04-MAR-2011 a second information request was submitted to the Applicant requesting responses to the following:
   a) A description of the methods used for maintaining the *B. cepacia* stock strain (ATCC 25416) used for validation of the detection assay.
   b) Clarification of whether the direct inoculation or membrane filtration method is used for validation of the detection procedure.
   c) Clarification of the procedures that will be used to verify the identity of colonies that grow on OFPBL test plates.
   d) Provision of a copy of the B. cepacia detection method, DPT-SOP-00686.

   An Amendment response (Supporting Document 36) was received 09-MAR-2011.

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Executive Summary

I. Recommendations

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

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – None.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is to be provided as a (b) (4) multi-dose nasal spray. The formulation includes (b) (4) phenylethyl alcohol and (b) (4) (b) (4) propylparaben. Microbial limits testing demonstrated that the product has a total aerobic microbial count of $< 10^2$ CFU/mL and a combined yeast and molds count of $< 10^1$ CFU/mL. It is free of *Staphylococcus aureus, Pseudomonas aeruginosa, and B. cepacia.*

B. Brief Description of Microbiology Deficiencies – No microbiology deficiencies identified.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A.

III. Administrative

A. Reviewer's Signature _____

Steven E. Fong, Ph.D.
Microbiology Reviewer

B. Endorsement Block _____

David Hussong, Ph.D.
Associate Director, New Drug Microbiology

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/s/

STEVEN E FONG
03/17/2011
Recommended for approval from a microbiology quality standpoint.

DAVID HUSSONG
03/18/2011
I concur with the reviewer's conclusion that the microbiology concerns have been addressed.

Product Quality Microbiology Review

07-MAY-2010

NDA 22-569/N-000.

Drug Product Name

Proprietary: PecFent® (name pending)
Non-proprietary: Fentanyl Nasal Spray

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
30-AUG-2009	31-AUG-2009	N/A	15-OCT-2009
17-FEB-2010	17-FEB-2010	N/A	N/A

Applicant/Sponsor

Name: Archimedes Development, Limited
Address: Nottingham Science and Technology Park
University Boulevard
Nottingham NG7 2TN
United Kingdom
Representative: Ann Tunstall
SciLucent, LLC
Telephone: 703-435-0033 X224

Name of Reviewer: Steven Fong, Ph.D.

Conclusion: Approvable pending resolution of microbiological deficiencies.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: NDA 505(b)(2).

2. SUBMISSION PROVIDES FOR: New drug product: [redacted] nasal spray [redacted]

3. MANUFACTURING SITE: [redacted]

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: [redacted], multi-dose nasal spray containing 1.57 mg/mL or 6.28 mg/mL fentanyl citrate salt.

5. METHOD(S) OF STERILIZATION: N/A. [redacted]

6. PHARMACOLOGICAL CATEGORY: Narcotic.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:

- The submission was provided electronically in CTD format.
- On 26-JAN-2010 an IR was sent to the applicant requesting microbiology quality information as detailed in review section P.5.1 (page 7, "Microbiology Specifications"). An amendment response (supporting document 8) was received 17-FEB-2010.
- On 08-MAR-2010 a second IR was sent to the applicant requesting that it test for *Burkholderia cepacia* in the Purified Water USP [redacted], provide a *B. cepacia* testing method, and revise the drug product specifications to indicate absence of *B. cepacia*. On 29-APR-2010 the applicant sent the RPM an e-mail indicating that a contract testing lab, [redacted] had devised a *B. cepacia* testing method, and that an amendment presenting the method and method validation would be provided on 07-JUN-2010. This date was beyond the point at which the information could be assessed in the current review cycle.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending resolution of microbiological deficiencies described in review section 3.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – None.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is to be provided as (b) (4), multi-dose nasal spray. The formulation includes (b) (4) phenylethyl alcohol and (b) (4) (b) (4) propylparaben. Microbial limits testing demonstrated that the product has a total aerobic microbial count of $< 10^2$ CFU/mL and a combined yeast and molds count of $< 10^1$ CFU/mL. It is free of *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

B. Brief Description of Microbiology Deficiencies – The applicant should amend the drug product specifications to state absence of *B. cepacia*, and provide a validated assay for detecting *B. cepacia* in the drug product and the USP water (b) (4) (b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies – Failure to address the product quality microbiology deficiencies could result in an increased risk of product contamination.

III. Administrative

A. Reviewer's Signature _____
Steven E. Fong, Ph.D.

B. Endorsement Block _____
David Hussong, Ph.D.
Associate Director, New Drug Microbiology

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

STEVEN E FONG
05/07/2010
Approvable pending resolution of microbiological deficiencies.

DAVID HUSSONG
05/12/2010
The testing requested by the reviewer is appropriate and information should be provided to the application is support of this testing.