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APPLICATION NUMBER:

201739Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

13-MAY-2011

NDA 201-739/N-000

Drug Product Name

Proprietary: Epinephrine Auto-Injector 0.15 mg

Epinephrine Auto-Injector 0.30 mg

Non-proprietary: Epinephrine Injection USP 1:1000

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
10-MAY-2011*	10-MAY-2011	N/A	N/A
10-MAY-2011*	10-MAY-2011	N/A	N/A
05-MAY-2011	05-MAY-2011	N/A	N/A
29-APR-2011	29-APR-2011	N/A	N/A
29-SEP-2010	29-SEP-2010	10-NOV-2011	10-NOV-2011

*Two amendments pertaining to microbiology quality, Supporting Documents 38 and 39, were received on 10-MAY-2011. As noted in Remarks items 4 and 5, these are referred to in the Review as the "10-MAY-2011a" and "10-MAY-2011b" Amendments, respectively.

Applicant/Sponsor

Name: Intelliject, Inc.

Address: 111 Virginia Street
Richmond, VA 23219

Representative: Joy K. Vander Wall
Senior Director, Regulatory Affairs
RRD International, LLC

Telephone: 301-762-6100 X119

Name of Reviewer: Steven Fong, Ph.D.

Conclusion: CMC-Microbiology recommends APPROVE.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA.
 2. **SUBMISSION PROVIDES FOR:** New drug product.
 3. **MANUFACTURING SITE:**
Drug Product Manufacturing Site
(b) (4)

Needle and Drug Cartridge Assembly Site
(b) (4)

Endotoxin and Sterility Testing Site
(b) (4)
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Solution Injection containing Epinephrine Injection USP 1:1000.
 - Total dose = 0.15 mg or 0.30 mg.
 - Administered intravenously with Auto-Injector device.
 5. **METHOD(S) OF STERILIZATION:** (b) (4).
 6. **PHARMACOLOGICAL CATEGORY:** Anti-allergen.
- B. **SUPPORTING/RELATED DOCUMENTS:**
- 1) DMF (b) (4) from (b) (4) describing manufacture of ready to sterilize, (b) (4).
 - 2) DMF (b) (4) from (b) (4) describing manufacture of ready to sterilize, (b) (4).
 - 3) LOAs dated 08-SEP-2010 from (b) (4) permitting Agency reviews of DMFs (b) (4).
 - 4) MAF (Device Master File) (b) (4) from Intelliject, Inc., describing the Epinephrine Auto-Injector device, and a LOA from Intelliject, Inc., dated 10-SEP-2010 permitting Agency review of the File.
 - 5) 13-MAY-2011 microbiology quality review of DMF (b) (4).
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C. REMARKS:

- 1) The Application was submitted electronically in CTD format.
- 2) On 26-APR-2011 the Reviewer sent an e-mail to Application representative Joy K. Vander Wal requesting the location of information in (b) (4) DMF (b) (4) pertaining to (b) (4). An Amendment response (Supporting Document 36) was provided 29-APR-2011 stating that the most recent update for (b) (4) was submitted 28-MAR-2011 (Page 11 of 32). The Amendment also clarified that (b) (4) and is not described in DMF (b) (4). Validation of (b) (4) was presented in the Amendment itself and is assessed in the current Review.
- 3) On 02-MAY-2011 the Reviewer sent a second e-mail to Ms. Vander Wal requesting the dates of submission Appendix G.5 and Section 13.2 in MAF (b) (4). An Amendment response, Supporting Document 37, was received 05-MAY-2011.
- 4) On 04-MAY-2011 the Reviewer recommended that Intelliject, Inc., amend the subject NDA with MAF (b) (4) Section (b) (4) and MAF (b) (4) Appendix (b) (4) so that this information could be assessed in the body of the NDA review. Such an amendment was possible because Intelliject, Inc., is the MAF holder as well as the NDA applicant. An Amendment response with the requested information, Supporting Document 38, was received 10-MAY-2011, and is referred to in this Review as the "10-MAY-2011a" Amendment.
- 5) On 09-MAY-2011 the following IR was sent to Intelliject, Inc.:

Regarding media fill simulations conducted in support of the subject NDA:

 - (1) *Please provide a justification for why media fill simulations are conducted in Room (b) (4) rather than the room proposed for product fill, Room (b) (4) 9. Are the fill processes and fill machinery in each room identical?*
 - (2) *Please identify the container closure system used for media fill. Is it identical to the (b) (4) system proposed for Epinephrine Injection USP 1:1000? If not please provide a justification.*
 - (3) *The text on page 24 of Section 3.2.P.3.5.4 states that (b) (4) is used for media fill, and that growth promotion studies for (b) (4) were conducted with (b) (4). However Table 3.2.P.3.5-4 (page 25) states that (b) (4) was utilized for simulation studies. Please clarify what medium was used. If (b) (4) was utilized please provide confirmation that this medium met growth promotion acceptance criteria.*

(4) *The acceptance criteria for fill simulation include a requirement that a minimum of (b) (4) containers be filled per trial (Section 3.2.P.3.5.4, Page 24). Table 3.2.P.3.5-5 presents results for simulations conducted with (b) (4). Please clarify why the number of (b) (4) filled in these trials is less than what is stipulated by the acceptance criteria.*

An Amendment response, Supporting Document 39, was received 10-MAY-2011, and is referred to in this Review as the “10-MAY-2011b” Amendment.

6) On 12-MAY-2011 the following IR was sent to Intelliject, Inc:

(1) *Validation protocol 7.5.1.17 (submitted in the 29-APR-2011 Amendment) states that the endotoxin level for (b) (4) (b) (4). Please clarify what this means in terms of allowable*

(2) *Please clarify whether validation is conducted on each and every batch of (b) (4) to verify that the endotoxin acceptance criterion has been achieved.*

7) On 12-MAY-2011 the Reviewer participated in a teleconference with representatives of Intelliject, Inc., to discuss the IR questions in Remarks Item 6. Responses to the questions are presented in the Review Section entitled *Validation of (b) (4)*

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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** – N/A

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - Following formulation bulk epinephrine 1:1000 product is passed through (b) (4)
- B. **Brief Description of Microbiology Deficiencies** – None.
- 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** _____
John Metcalfe, Ph.D.
Senior Microbiology Reviewer
- C. **CC Block**—N/A

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/s/

STEVEN E FONG

05/13/2011

Recommended for approval from a microbiology quality standpoint.

JOHN W METCALFE

05/13/2011

I concur.