

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201923Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

25-JUL-2011

**NDA 201-923/N-000**

**Drug Product Name**

**Proprietary:** Iluvien®

**Non-proprietary:** Fluocinolone acetonide intravitreal insert

**Review Number:** 2

**Dates of Submission(s) Covered by this Review**

Submit	Received	Review Request	Assigned to Reviewer
12-MAY-2011	12-MAY-2011	23-MAY-2011	27-MAY-2011

**Submission History (for amendments only)**

Submit Date(s)	Microbiology Review #	Review Date(s)
30-JUN-2010	1	08-DEC-2010

**Applicant/Sponsor**

**Name:** Alimera Sciences, Inc.

**Address:** 6120 Windward Parkway, Suite 290  
Alpharetta, GA 30005

**Representative:** Barbara H. Bauschka  
Director, Regulatory Affairs

**Telephone:** 678-527-1330

**Name of Reviewer:** Steven Fong, Ph.D.

**Conclusion:** CMC-Microbiology recommends APPROVE.

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## Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA.

2. **SUBMISSION PROVIDES FOR:** New drug product.

3. **MANUFACTURING SITE:**

Drug Substance Manufacturing Site: Drug Product Manufacturing Site:



4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**

- 3.5 mm long, composite rod (b) (4) composed of 0.19 mg Fluocinolone acetonide (FA) drug substance mixed with (b) (4) polyvinyl alcohol (PVA). (b) (4)
- Rod provided within a hand piece inserter device.
- (b) (4) rod pushed through a 25 gauge needle into the vitreous of the eye with the aid of inserter device.

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

6. **PHARMACOLOGICAL CATEGORY:** Diabetic edema therapeutic.

B. **SUPPORTING/RELATED DOCUMENTS:**

- 09-FEB-2011 microbiology quality review of an Applicant meeting package provided 18-JAN-2011.

C. **REMARKS:**

- The subject NDA was provided electronically in CTD format.
- The subject NDA was initially submitted 30-JUN-2010. Multiple deficiencies pertaining to (b) (4) controls and testing procedures were identified in a 08-DEC-2010 microbiology quality review of the Application. These were cited as deficiencies 2a, 2b, 2h, 2i, 2j, 2k, and 2l in a CR letter issued 22-DEC-2011.

- Deficiencies cited in the CR letter were addressed in a meeting package submitted 18-JAN-2011, and were discussed in a face-to-face meeting with the Applicant on 22-DEC-2011. A review of the meeting package was submitted by the Reviewer on 09-FEB-2011.

**filename:** N201923r2.doc

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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** – Drug product rods consisting of (b) (4) mixture of FA drug substance and PVA in polyimide tubes are inserted into guide shafts. The guide shafts are assembled into hand piece inserter devices that are in turn packaged into (b) (4) trays with (b) (4) lids. The packages are packed into (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



(b) (4)

—Acceptable—

*Comment.* (b) (4)

**Deficiency 2h.** The manufacturing process should be modified to include (b) (4) product bioburden testing, and the (b) (4) quality control parameters should be amended to include product bioburden alert and action levels. Excessive bioburden in the Fluocinolone acetonide (FA) rods could contaminate the product with microbial toxins, debris, and metabolites. These contaminants (b) (4) should be controlled for.

Resubmission Response. The manufacturing process has been modified to include (b) (4) product bioburden testing, and the (b) (4) quality control parameters have been amended (b) (4)

(b) (4)

The results presented in Report 11004 showed that the FA rod extract had no detectable inhibitory effect on the growth of the test microorganisms.

—Acceptable—

**Deficiency 2i.** The proposed hold period is not acceptable. Please provide a description of the bioburden and endotoxin testing procedures performed (b) (4)

(b) (4)  
**Presentation of study results without including the details of how they were performed is not acceptable.**

Resubmission Response. The specific proposed hold period is (b) (4)

The proposed period is based on studies executed (b) (4)  
Summaries of the endotoxin and bioburden testing procedures are presented above, respectively, in the responses to Deficiencies 2b and 2h. As noted in the original submission, for all 3 batches the bioburden was determined (b) (4)  
These data met the acceptance criteria (b) (4) and justified the proposed hold periods.

—Acceptable—

**Deficiency 2j. The description of the (b) (4) procedure is not complete. Please describe (b) (4) the procedure (b) (4)**

Resubmission Response. The procedure (b) (4) was presented (b) (4)  
each FA drug rod is placed into a guide shaft subassembly that is in turn assembled into a hand piece subassembly. The completed unit is placed into a (b) (4) tray that is sealed with a (b) (4) lid and placed into a unit carton. (b) (4)

—Acceptable—

**Deficiency 2k. The (b) (4) studies should be conducted under the conditions to be used (b) (4) Please provide the procedures, acceptance criteria, and data sets (b) (4)**

Resubmission Response. (b) (4)



(b) (4)  
 This range was within the (b) (4)  
 acceptance criterion.

—Acceptable—

**Deficiency 2l. The descriptions of the procedures for bioburden determination, sterility testing and bacteriostasis-fungistasis testing are not complete. Please provide the procedures for bioburden determination, sterility testing, and bacteriostasis-fungistasis testing that were carried out in support of (b) (4) verification studies.**

Resubmission Response. A summary of the requested test methods is presented below in Table 1. Documents for each of the entries indicated under “Test Method” in the table were included with the Resubmission. The procedures for assessing bioburden and sterility in the FA rods (b) (4) are the same as those described above in the response to Deficiency 2h. The procedures for conducting bacteriostasis-fungistasis testing are also described in the Deficiency 2h response.

TABLE 1. Summary of Methods Used for Bioburden, Sterility and Bacteriostasis-Fungistasis Testing\*

Test Method	Title	Location
MTM-200030	Microbial Bioburden Determination	3.2.P.5.2
PTS-200567	Specific Bioburden Test Instruction for Alimera Product – Iluvien (b) (4)	3.2.P.5.2
MTM-200042	Bacteriostasis and Fungistasis Testing	3.2.P.5.2
MTM-200087	Sterility Testing of Medical Devices	3.2.P.5.2

\*This table is a copy of Table 3 within Resubmission Section 1.11.1—Quality Information Amendment.

—Acceptable—

**3. LIST OF MICROBIOLOGY DEFICIENCIES AND  
COMMENTS: None.**

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/s/  
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STEVEN E FONG

07/25/2011

Recommended for approval from a microbiology quality standpoint.

JOHN W METCALFE

07/25/2011

I concur.

**OPS-MICROBIOLOGY REVIEW OF NDA MEETING PACKAGE  
(NDA 201-923/N-000)**

**I. NDA: 201-923/N-000**

**REVIEW DATE:** 9-FEB-2011  
**MICROBIOLOGIST:** Steven Fong  
**DRUG NAME:** Iluvien® (Fluocinolone acetonide intravitreal insert)  
**SPONSOR:** Alimera Sciences, Inc.  
**DOCUMENT DATE:** 23-DEC-2010      **CONSULT DATE:** 19-JAN-2011  
**DATE ASSIGNED:** 19-JAN-2011  
**DOSAGE FORM:** 3.5 mm long composite rods consisting of 0.19 mg Fluocinolone acetonide mixed with polyvinyl alcohol. The rods are inserted into the vitreous of the eye with a hand held inserter device.

**II. MANUFACTURER:**

Drug Product Manufacturing Site: (b) (4)  
(b) (4)

**III. REVIEW NOTES:**

**1. BACKGROUND**

On 23-DEC-2010 Alimera Sciences, Inc. submitted a request for a face-to-face, Type A meeting with the Agency to discuss a Complete Response that was issued 22-DEC-2010 for its NDA 201-923/N-000 submission. The request was granted 30-DEC-2010, a meeting package was provided 18-JAN-2011, and responses to questions in the meeting package were sent to the Applicant 28-JAN-2011 and 02-FEB-2011. The meeting was held 02-FEB-2011.

The subject NDA proposes treatment of diabetic edema with Fluocinolone acetonide (FA) impregnated, solid polyvinyl alcohol (PVA) rods injected into the vitreous of the eye with an inserter device (b) (4) each rod consists of 0.19 mg of FA mixed with (b) (4) PVA. (b) (4)

(b) (4) During manufacture the rods are inserted into guide shafts that are in turn assembled into hand piece inserter devices. The devices are packaged into (b) (4) trays sealed with (b) (4) lids (b) (4)

On 08-DEC-2010 the Reviewer submitted a microbiology quality review of the Application that identified seven deficiencies regarding bioburden control parameters, product hold period, (b) (4) microbiology quality testing procedures, and endotoxin specification.

## 2. DISCUSSION

The Meeting Package included one question (Question 6.2) pertinent to microbiology quality. The question referred to two deficiencies (deficiencies 6 and 7) cited in the Reviewer's 08-DEC-2010 review, and is presented below in italic font. The Agency response is presented in bold type.

### Question 6.2

[Deficiency 6 from 08-DEC-2010 microbiology review]. *The currently proposed limit (b) (4) is not applicable to the solid dose FA drug product. Without an appropriate descriptor for expressing product endotoxin limit, the acceptability of the proposed limit cannot be evaluated. Please modify the endotoxin limit value so that it is based on a per drug rod or per mg (b) (4)*

[Deficiency 7 from 08-DEC-2010 microbiology review]. *The testing method presented in attachment MTM-200033 represented only a general SOP for LAL gel clot testing, and did not include procedures and data sets relevant to FA drug product. The stability test results (b) (4) are not acceptable without an adequate description of the endotoxin testing procedure and appropriate acceptance criteria. Please provide a description of the endotoxin testing procedure as it applies to FA drug product. The description should include the method by which the drug product rods are prepared for sampling, and the procedures and data sets for interference/enhancement testing.*

*Alimera is preparing an analytical procedure, which will also be validated, for endotoxin testing specific to Iluvien. This method will be based on the unit (b) (4). The appropriate specification revision will also be made.*

*Will this analytical procedure, specific to the unit, address the Agency's comments?*

### Agency Response

**A unit specific analytic procedure is acceptable. The method should provide the specific procedures and acceptance criteria to be used for Iluvien drug product, and conform to the requirements of USP <85>.**

Topics related to microbiology quality were not discussed at the 02-FEB-2011 face-to-face meeting.

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Steven Fong, Ph.D.  
Review Microbiologist

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John Metcalfe, Ph.D.  
Senior Microbiologist

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/s/  
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STEVEN E FONG  
02/09/2011

JOHN W METCALFE  
02/09/2011

# Product Quality Microbiology Review

08-DEC-2010

**NDA 201-923/N-000**

**Drug Product Name**

**Proprietary:** Iluvien®

**Non-proprietary:** Fluocinolone acetonide intravitreal insert

**Review Number: 1**

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
30-JUN-2010	30-JUN-2010	30-JUN-2010	30-JUN-2010

**Applicant/Sponsor**

**Name:** Alimera Sciences, Inc.

**Address:** 6120 Windward Parkway, Suite 290  
Alpharetta, GA 30005

**Representative:** Barbara H. Bauschka  
Director, Regulatory Affairs

**Telephone:** 678-527-1330

**Name of Reviewer:** Steven Fong, Ph.D.

**Conclusion:** Approvable pending resolution of microbiological deficiencies.

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA.
  2. **SUBMISSION PROVIDES FOR:** New drug product.
  3. **MANUFACTURING SITE:**

Drug Substance Manufacturing Site: Drug Product Manufacturing Site:

(b) (4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**

- 3.5 mm long, composite rod (b) (4) composed of 0.19 mg Fluocinolone acetonide (FA) drug substance mixed with (b) (4) polyvinyl alcohol (PVA). (b) (4)
- Rod provided within a hand piece inserter device.
- (b) (4) rod pushed through a 25 gauge needle into the vitreous of the eye with the aid of inserter device.

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

6. **PHARMACOLOGICAL CATEGORY:** Diabetic edema therapeutic.

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:**

- The subject NDA was provided electronically in CTD format.
- The submission was granted priority review status with a 6 month review clock.

**filename:** N201923r1.doc



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## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability** – Approvable pending resolution of microbiological deficiencies.
- 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** – Drug product rods consisting of (b) (4) mixture of FA drug substance and PVA in polyimide tubes are inserted into guide shafts. The guide shafts are assembled into hand piece inserter devices that are in turn packaged into (b) (4) trays with (b) (4) lids. (b) (4)
- B. Brief Description of Microbiology Deficiencies** – The applicant should: (1) include (b) (4) and impose (u) (4) bioburden alert and action limits; (2) describe the bioburden and endotoxin testing procedures used (b) (4); (3) describe (u) (4) the procedure (u) (4); (4) provide the procedures, acceptance criteria and data sets (b) (4); (5) provide the procedures for bioburden determination, sterility testing, and bacteriostasis-fungistasis testing carried out (b) (4); (6) modify the endotoxin limit value so that it is based on a per drug rod (b) (4); and (7) provide a description of the FA endotoxin testing procedure.
- 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.,  
Microbiology Reviewer
- B. Endorsement Block** \_\_\_\_\_  
John Metcalfe, Ph.D.  
Senior Microbiology Reviewer
- C. CC Block—N/A**



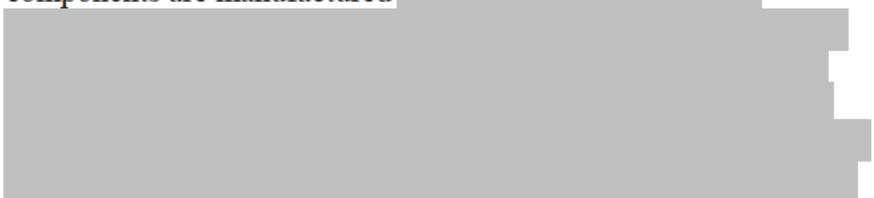
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## **Product Quality Microbiology Assessment**

### **1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA**

#### **P DRUG PRODUCT**

##### **P.1 Description of the Composition of the Drug Product**

- **Description of drug product** – The drug product is a 3.5 mm long, solid rod consisting of 0.19 mg of FA drug substance mixed with (b) (4) PVA. (b) (4)  

- **Drug product composition** – The drug product composition was presented in Table 1 in Submission Section 3.2.P.1. Each 3.5 mm drug product rod contains 0.19 mg FA drug substance mixed with (b) (4) PVA.
- **Description of container closure system** – A description of the container closure system was provided in Submission Section 3.2.P.7. The 3.5 mm drug product rods are placed into a guide shaft subassembly that is in turn assembled into a hand piece subassembly. The completed unit is placed into a (b) (4) tray that is sealed with a (b) (4) lid and placed into a unit carton. (b) (4)  

  - **Container Closure Illustrations.** Detailed drawings of the guideshaft and hand piece subassemblies were presented in Attachments DWG-06-114-001, DWG-06-114-004, DWG-06-114-010, DWG-06-114-011, DWG-06-114-012, DWG-06-114-013, DWG-06-114-05-001, DWG-06-114-05-002, DWG-06-114-09-004, DWG-06-114-09-005, DWG-06-114-11-003, DWG-06-114-11-004, DWG-06-114-11-005, DWG-06-114-11-006.
  - **Guideshaft Subassembly Materials.** The inserter device components are manufactured (b) (4)  


(b) (4)

➤ Hand Piece Sub-assembly Materials. The hand piece sub-assembly is

(b) (4)

**P.2 Pharmaceutical Development**

**P.2.5 Microbiological Attributes**

- **Container Closure and Package integrity** – Container closure integrity of the (b) (4) tray (b) (4) lid system was tested by the dye ingress method (b) (4). Procedures and data sets for testing were presented in attachment DP2009-203 within Submission Section 3.2.P.5.3. To conduct analysis, 9 groups of containers from product lot W0004979 were utilized.

(b) (4)

*[Text continued on Review Page 7]*

TABLE 1. Results of Methylene Blue Dye Ingress Testing Conducted with (b) (4) Tray (b) (4) Lid Containers\*

Sample #	(b) (4)
Group 1	
Group 2	
Group 3	
Group 4	
Group 5	
Group 6	
Group 7	
Group 8	
Group 9	

\* This table is a copy of Table 1 in submission Attachment DP2009-203. Each group contained 10 test samples and 6 positive control samples.

(b) (4)

Together, the data indicate that the (b) (4) tray (b) (4) lid system Taken can effectively resist microbial ingress under the room temperature, ambient humidity and pressure conditions proposed for storage.

—Acceptable—

- (b) (4)
- **Justification for not having a microbial limit specification for a non-sterile drug product** – N/A. Product is sterile.

**P.3 Manufacture**

**P.3.1 Manufacturers**

The identity and location of the drug substance manufacturing, drug product manufacturing, (b) (4) are presented above in Review Section A.3 (Review Page 2).

**P.3.3 Description of the Manufacturing Process and Process Controls**

A description of the manufacturing process was provided in Submission Section 3.2.P.3.3. This description included a schematic (Section Figure 3) of the production process. (b) (4)

(b) (4)

maximum time limit (b) (4) was not specified.

—Not Acceptable—

*Comment 1. Excessive bioburden in the FA rods could contaminate the product with microbial toxins, debris, and metabolites.* (b) (4)

*The manufacturing process should be modified to*

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/s/  
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STEVEN E FONG

12/08/2010

Approvable pending resolution of microbiological deficiencies.

JOHN W METCALFE

12/08/2010

I concur.

# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number: 201-923/N-000 Applicant: Alimera Sciences, Inc. Letter Date: 28-JUN-2010**

**Drug Name: Iluvien® (Fluocinolone acetonide intravitreal insert) NDA Type: Original NDA Stamp Date: 30-JUN-2010**

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

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Submission provided electronically in CTD format.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Sections 2.3.P and 3.2.P.3.3
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Section 3.2.P.3.5
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	Submission was provided in English.
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Container closure integrity described in section 3.2.P.2.4.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Sections 2.3.P.5.1 and 3.2.P.5.1 (Table 1).
7	Has the applicant submitted the results of analytical method verification studies?	X		Sections 2.3.P.5.1.4, 2.3.P.5.1.5, 3.2.P.5.2, and 3.2.P.5.3.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	N/A	N/A	Pre-submission microbiology quality requests were not made.
9	Is this NDA fileable? If not, then describe why.	X		

**Additional Comments:** The drug product consists of 3.5 mm long rods of Fluocinolone acetonide drug substance mixed (b) (4) with (b) (4) polyvinyl alcohol. The rods are provided within inserter devices with 25 gauge extra-thin wall needle attachments. The rod-inserter device assemblies are packaged within trays that are sealed with (b) (4) lids, packed into cartons, (b) (4) During drug administration, the rods are pushed into the vitreous of the eye with the aid of the inserter device.

Steven Fong, Ph.D.	30-JUL-2010
Reviewing Microbiologist	Date

John Metcalfe, Ph.D.	30-JUL-2009
Microbiology Secondary Reviewer	Date



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201923	ORIG-1	ALIMERA SCIENCES INC	FLUOCINOLONE ACETONIDE INTRAVITREAL INSERT 0.19 mg

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/s/

STEVEN E FONG

07/30/2010

Application is approved for filing from a microbiology quality standpoint.

JOHN W METCALFE

07/30/2010

I concur.