

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206911Orig1s000**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**



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

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**DATE:** 15 April 2016

**TO:** File: 206911

**FROM:** Jonathan G. Swoboda, PhD, RAC  
Review Microbiologist  
CDER/OPQ/OPF/Division of Microbiology Assessment

**THROUGH:** Dupeh Palmer, PhD  
Senior Review Microbiologist  
CDER/OPQ/OPF/Division of Microbiology Assessment

**SUBJECT:** NDA: 206911  
Submission Date: 11 March 2016  
Drug Product: Bromfenac Ophthalmic Solution  
Applicant: InSite Vision Incorporated

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**Background:** A product quality microbiology review of NDA 206911 was completed on 22 January 2016. Reference is made to concerns regarding antimicrobial effectiveness test (AET) failures on stability with Bromfenac ophthalmic multi-dose drug products containing (b) (4) and (b) (4). To this end, the Division of Microbiology Assessment (DMA) recommended a commitment to perform routine AET during post-approval stability under long-term conditions (i.e., 25°C/50% RH) and to provide AET results for the current exhibit batch on stability at 30 months. Prior to completing the microbiology review, the applicant committed to routine AET for post-approval stability (see original microbiology review). The AET results for the 30 month results were not available at the time. The subject of this microbiology memo is the evaluation of AET results provided for the existing stability lots at the 30 month time point.

**Microbiology Review:** In the subject amendment, the applicant provides results demonstrating all three registration lots (lot numbers: 00313B, 00313C, and 00313D), passed requirements for AET per USP <51> at the 30 month time-point. Sterility results per USP<71> for this time point were not provided. Sterility testing is performed annually and successful 24 month sterility results were provided.

**Reviewer's Assessment:** The previous DMA recommendation for approval from a sterility assurance perspective remains. (b) (4)  
(b) (4) Sterility results per USP<71> at this time period is not required since annual sterility testing per USP<71> is performed, and acceptable results are provided at 24 months.

**END**

MEMORANDUM

Jonathan Swoboda  
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# Product Quality Microbiology Review

22 January 2016

**NDA:** 206911

**Drug Product Name**

**Proprietary:** BromSite™

**Non-proprietary:** Bromfenac Ophthalmic Solution

**Review Number:** 1

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

Submit	Received	Review Request	Assigned to Reviewer
10 JUN 2015	10 JUN 2015	N/A	17 JUL 2015
21 OCT 2015	21 OCT 2015	N/A	N/A
20 JAN 2016	20 JAN 2016	N/A	N/A

**Applicant/Sponsor**

**Name:** InSite Vision Incorporated

**Address:** 965 Atlantic Ave.  
Alameda, CA 94501

**Representative:** Kamran Hosseini, MD, PhD  
VP Clinical and Regulatory Affairs/Chief Medical Officer



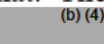


**Telephone:** 510-747-1264; **Fax:** 510-865-4375

**Name of Reviewer:** Jonathan G. Swoboda, PhD, RAC

**Conclusion:** The submission is recommended for approval on the basis of sterility assurance.

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** 505(b) (2) Original NDA
  2. **SUBMISSION PROVIDES FOR:** Initial marketing of a sterile drug product.
  3. **MANUFACTURING SITE:**  (b) (4)
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Sterile, multi-dose, ophthalmic solution (0.075% w/w)
    - 7.5 mL plastic bottles with dropper tips and caps
    - Topical administration
  5. **METHOD(S) OF STERILIZATION:**  (b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** The subject drug product is used for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.
- B. **SUPPORTING/RELATED DOCUMENTS:** Not applicable
- C. **REMARKS:**  
The application is provided as an electronic submission in E-CTD format. The microbiology reviewer participated on the Pre-Approval Inspection of  (b) (4)  during the week of  (b) (4). Information requests were sent to the applicant on 18 September 2015 and 23 December 2015. Responses to these comments from the 21 October 2015 and 20 January 2016 submissions are reviewed below.

Filename: 206911.doc

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**Executive Summary**

**I. Recommendations**

- A. Recommendation on Approvability** - The submission is **recommended** for approval on the basis of sterility assurance.
  
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable

**II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – (b) (4)

(b) (4)

- B. Brief Description of Microbiology Deficiencies** – Microbiology deficiencies have not been identified.
  
- C. Contains Potential Precedent Decision(s)**-  Yes  No

**III. Product Quality Microbiology Risk Assessment**

- A. Initial Product Quality Microbiology Risk Assessment**

(b) (4)

**Reviewer’s comment:** The sterilization process is a combination of (b) (4). For the risk assessment above, a worst-case value was established based on (b) (4).

**B. Final Risk Assessment** - The production of the sterile drug product does not pose patient risk from a microbiology perspective.

**IV. Administrative**

**A. Reviewer's Signature** \_\_\_\_\_

**B. Endorsement Block**

Microbiologist/Jonathan G. Swoboda, PhD, RAC  
Microbiology Quality Assessment Lead (Acting)/John W.  
Metcalf, PhD

**C. CC Block**

In Panorama

**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 subject drug product is a translucent, yellow, viscous, sterile solution packaged in a plastic dropper bottle.
- Drug product composition –

<b>Ingredients</b>	<b>Function</b>	<b>Concentration (%w/w)</b>
Bromfenac Sodium Sesuihydrate	Active pharmaceutical ingredient (API)	0.075
Boric Acid, NF		(b) (4)
Sodium Borate, NF		(b) (4)
Citric Acid Anhydrous, USP		(b) (4)
Sodium Citrate Dihydrate, USP		(b) (4)
Poloxamer 407, NF		(b) (4)
Benzalkonium Chloride, NF	Preservative	(b) (4)
Polycarbophil, USP		(b) (4)
Sodium Chloride, USP		(b) (4)
Edetate Disodium Dihydrate, USP		(b) (4)
(b) (4) Sodium Hydroxide, NF	pH adjusting agent	Adjust to pH 8.3
Water for Injection (WFI), USP		(b) (4)

- Description of container closure system – The bottles [7.5 mL low density polyethylene (LDPE) bottles (5 mL fill volume)] are formed using (b) (4) of LDPE dropper tips, closed with high density polyethylene (HDPE) dropper caps, and LDPE tamper-evident over seals. (b) (4) are enclosed in a (b) (4) sealed laminated (b) (4) foil pouch. The (b) (4)

**P.2 Pharmaceutical Development**

**P.2.5 Microbiological Attributes**

- Container-Closure and Package integrity – Container-closure integrity testing (CCIT) was performed using microbial ingress with *Brevundimonas diminuta* (Section: 3.2.P.7; Document number: V13-002-00R). The studies were carried out using a “5 mL” bottle as opposed to the 7.5 mL bottle proposed for production. There is no indication as to how the “5 mL” bottle represents the bottle proposed for production. Media filled bottles were used for CCIT [30 test bottles, 3 positive control bottles (pierced with a 25G needle), and 3 negative control bottles]. The LDPE



tamper-proof over seal was removed prior to testing. The test and positive control vials were submerged in a microbial bath of *B. diminuta* (Challenge concentration:  $1.74 \times 10^7$  CFU/mL), subjected to a vacuum of 20 inches of Hg for 30 minutes followed by 15 minutes at atmospheric pressure, and incubated (with negative control samples) to evaluate bacterial growth. All test and negative control samples did not demonstrate growth, while the positive control samples demonstrated growth.

- (b) (4) Testing – (b) (4) was validated per protocol number V13-018-00-R, and the validation results are presented in Section 3.2.P.5.3. The preservative, benzalkonium chloride (BAC), specifications for release and stability are (b) (4) and (b) (4) respectively. (b) (4) was performed per (b) (4) using various concentration of BAC (b) (4) % to 0.005% BAC as well as a (b) (4). The (b) (4) performed with a BAC concentration of (b) (4) % met the acceptance criteria outlined in (b) (4), and the sample (b) (4) formulation failed (b) (4) requirements (Section 3.2.P.2; (b) (4) % (b) (4) Test Report.pdf”).

The applicant also performed a simulated use test. Samples were manipulated twice a day for 32 days (twice the duration of typical use). Following the test period, negative control samples, which were not manipulated, and test samples were subject to AET. Both sets of samples met USP<51> requirements (Section: 3.2.P.8.3; Document number: V12-018.00R).

*Information request sent on 18 September 2015:*

1. *On page 8 of 64 in the document entitled, “V13-002-00R – Validation Report for ISV-303 Container Closure Integrity Test (Microbial Ingress).pdf,” it is stated that a 5.0 mL bottle was used for the container-closure integrity studies. However, commercial production proposes the use of a 7.5 mL bottle. Provide container-closure integrity results from studies performed using the proposed container-closure for the commercial production of the subject drug product (i.e., 7.5 mL bottle).*

Summary of response received in the 21 October 2015 submission: The applicant clarifies that the “5.0 mL” and “7.5 mL” bottles are the same. The bottle capacity is 7.5 mL; however, the typical fill volume is 5.0 mL.

### Acceptable

**Reviewer’s comment:** The applicant has provided sufficient results demonstrating the integrity of the container-closure as a microbial barrier and the microbial efficacy of the preservative upon release. AET results, following simulated use, indicate the preservative remains active, per USP<51> after 32 days.

(b) (4)

**P.5 Control of Drug Product****P.5.1 Specifications**

The subject drug product must be sterile upon release; however, an endotoxin specification is not required since the drug product is a topical ophthalmic solution.

**P.5.2 Analytical Procedures**

- **Sterility –**

The sterility test is carried out using test method TM800 per USP<71> using membrane filtration with lot number 01512B of the subject drug product. The validation studies were performed by Insite Vision Inc. and the results are provided in document number V12-012.00R (Section: 3.2.P.5.3). Test and positive control samples were inoculated with compendial microorganisms. Similar growth was observed between test and positive control samples. Sterility testing performed on stability registration batch numbers 00313-B, -C, and -D indicate the batches were sterile upon release.

*Information request sent on 18 September 2015:*

10. On page 1 of 2 in the document entitled, “Manufacturer(s) (b) (4).pdf,” it is indicated that the (b) (4) will perform product release and stability testing. Clarify whether this facility performed the sterility test validation study provided in Section 3.2.P.5.3 (Report number: V-12-012-00-R). If not, provide results from sterility test validation studies for all facilities that will perform sterility testing of the subject drug product for release and stability.

Summary of response received in the 21 October 2015 submission: The applicant clarifies that (b) (4) will perform routine sterility testing for release. Sterility testing for stability studies will be performed at (b) (4). Suitability testing, per USP<71>, has been successfully performed at the (b) (4) facility (Document number: RDPCL548) and by the applicant, Insite Vision Inc. (Document number: V-12-012-00-R; described above). The applicant commits to performing method validation at the (b) (4) facility prior to the initiation of commercial production. Since successful suitability testing has been performed for the subject drug product, additional verification testing at the (b) (4) facility is not necessary.

**Acceptable**

**Reviewer’s comment:** The applicant has provided successful results verifying release and stability sterility testing per USP<71>.

**P.7 Container Closure System – See P.1**

**P.8 Stability****P.8.1 Stability Summary and Conclusion**

The proposed expiration date is <sup>(b) (4)</sup> months (based on the 12 month stability results) <sup>(b) (4)</sup>

The drug product must remain sterile over the course of the stability study. Stability studies were conducted under long-term (25°C/40% RH) conditions. Sterility testing is performed initially and then annually through 36 months. The registration batch numbers 00313-B, -C, and -D were sterile under long-term conditions up to 12 months.

**P.8.2 Post-Approval Stability Protocol and Stability Commitment**

The applicant states that the first three commercial production batches will be placed on a long-term stability program. Every year thereafter, one production batch will be added to the program.

**P.8.3 Stability Data**

See Section P.8.1.

*Information request sent on 23 December 2015:*

*The FDA is aware of issues with antimicrobial effectiveness testing (AET) failures of multiple dose topical ophthalmic products preserved with benzalkonium chloride. The cause of these AET failures is presently unknown. The FDA is requesting additional information regarding preservative effectiveness testing for some multiple dose topical ophthalmic products in order to ensure that the preservative is not only present, but effective throughout the product shelf-life. Once a satisfactory preservative effectiveness history has been established, modified stability test schedules and expiration dating may be requested of the Agency. Provide the following information:*

- Revise the proposed expiration date for bromfenac ophthalmic solution to a time point at which the drug product has been demonstrated to pass AET per USP <51> or an equivalent method.*
- Provide AET results from product lots that are currently in the stability program.*
- Include the USP <51> or equivalent AET as a routine test for all stability lots according to the test schedule provided in ICH Q1A(R2) Section 2.2.6.*

**Summary of response received in the 20 January 2016 submission:** The applicant confirms that AET was not proposed for post-approval stability studies. However, AET was to be performed on the registration batches (Batch numbers: 00313-B, -C, and -D) at <sup>(b) (4)</sup> proposed expiry <sup>(b) (4)</sup> months). The applicant commits to performing an AET study at 30 months for the registration batches. The results were not provided at the time of this review; however, they will be submitted once they are available. The applicant also commits to performing annual AET post-approval. AET is performed using internal method TM801 per USP<51>. Despite not providing AET results for the registration batches; the AET testing frequencies are sufficient to minimize patient exposure to drug product that fails AET. Additional information will not be requested.

**Acceptable**

**Reviewer's comment:** The applicant has provided acceptable results and information to support the shelf life from a microbiology perspective per the Agency's requirements.

**R REGIONAL INFORMATION**

**R.1 Executed Batch Record**

Batch records have been provided for registration batch numbers 00313-B, -C, and -D in Section 3.2.R.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-  
QUALITY (CTD-Q)  
MODULE 1**

**A. PACKAGE INSERT**

The following storage conditions are indicated in the package insert: store at 15 – 25°C (59 – 77°F).

**Acceptable**

**END**

Jonathan  
Swoboda -S

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