CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206911Orig1s000

CHEMISTRY REVIEW(S)

NDA 206911

Product Quality Assessment (Addendum #1 to Review #1)

From: Chunchun Zhang, ATL/Acting CMC Lead, Branch 3, ONDP

Date: April-8-2016

Re: Amendment submitted on March 11, 2016/24 months shelf life for the proposed drug product

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The applicant submitted an Amendment dated on March 11, 2016 which provided stability update up to 30-months. In this Amendment, the applicant requested a (b) (4)

The requested (b) (4) cannot be granted because of the observed (b) (4) but the stability data submitted supports an expiration dating of 24 months. Therefore, a 24-month shelf-life is recommended when the drug product is stored at 15-25°C in the proposed container closure system.

OPQ's Review #1 recommended Approval and this Addendum upholds the **Approval** recommendation from Product Quality perspective.

Chunchun Zhang, Ph.D.
ATL for 206911

Chunchun Zhang -S

Digitally signed by Chunchun Zhang -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chunchun Zhang -S, 0.9.2342.19200300.100.1.1=2001178137
Date: 2016.04.08 13:18:07 -04'00'

Recommendation:
NDA: Approval

NDA 206911
Review #1
March 4, 2016

Drug Name/Dosage Form	Bromfenac ophthalmic solution
Strength	0.075% w/w
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	InSite Vision Incorporated
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	10-Jun-2015
Amendment	4-Sep-2015
Amendment	24-Sep-2015
Amendment	21-Oct-2015
Amendment	10-Dec-2015
Amendment	20-Jan-2016
Amendment	26-Feb-2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Katherine Windsor, Ph.D.	ONDP/ DNDAPI/ Branch 1
Drug Product	Chunchun Zhang, Ph.D.	ONDP/DNDP-I/Branch III
Process	David Dean Anderson, Ph.D.	OPF/DPAIII/PABVII
Microbiology	Jonathan G. Swoboda, PhD, RAC	OPF/DMA/Branch III
Facility	Frank Wackes. Ph. D.	OPF/DIA/IABII
Biopharmaceutics	Om Anand, Ph.D.	ONDP/DBP/Branch I
Regulatory Business Process Manager	Erin Andrews, Pharm D	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang, Ph. D.	ONDP/DNDP-I/Branch III
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Covered by DP review	

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	2/25/2016	Reviewed by Katherine Windsor; LoA: 12/18/2012
	Type V			Adequate	12/02/2015	LoA: 11/20/2013
	Type IV			N/A		LoA: 9/19/2011

[1]Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107723	This product during IND development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		8/28/2015	Aaron Ruhland
CDRH	NA			
Clinical	NA			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 206911 is recommended for approval from the Product Quality perspective. CMC-related labeling recommendations have been provided to the OND PM for consideration during final labeling.

1. Summary of Complete Response issues: Not Applicable

2. Action letter language, related to critical issues such as expiration date
   "An expiration dating period of (b)(4) months is approved for Bromfenac ophthalmic solution, 0.075% when packaged and stored as described in the attached labeling."

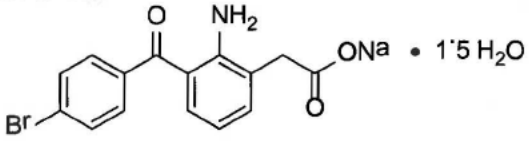
3. Benefit/Risk Considerations
   Evaluation of the quality aspects of Bromfenac ophthalmic solution, 0.075% supports approval without consideration of specific benefit/risk aspects.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. None

II. Summary of Quality Assessments

A. Drug Substance [Bromfenac Sodium] Quality Summary

The applicant cross-referenced the CMC information for bromfenac sodium drug substance to DMF (b)(4). DMF (b)(4) was reviewed by Katherine Windsor, Ph.D. (final signature 25-FEB-2016) and was found adequate to support NDA 206911.



Bromfenac sodium (sodium 2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate) is a member of the phenylacetic acid class of non-steroidal anti-inflammatory drugs (NSAIDs) and has been used in other FDA approved ophthalmic solutions (Prolensa, Bromday, and Xibrom – discontinued for business reasons). This drug substance is a bright orange to yellow powder of a (b)(4). Bromfenac is adequately soluble (≥ 0.5% w/w) over the pH range of (b)(4) to achieve the target drug product concentration of 0.075%. Stability data from the DMF holder support a retest period of (b)(4) months for bromfenac sodium drug substance manufactured at (b)(4) (b)(4) and stored at (b)(4)

B. Drug Product [Bromfenac ophthalmic solution] Quality Summary

Bromfenac ophthalmic solution, 0.075% drug product is a sterile, preserved, (b) (4), viscous, multidose eye drop packaged in 7.5 mL white low density polyethylene (LDPE) bottles (5 mL fill) with clear LDPE dropper tips, gray high density polyethylene (HDPE) dropper caps and white LDPE tamper-evident overseal. Additionally, each bottle is enclosed in a (b) (4) sealed laminated (b) (4) foil pouch.

All components are compendial. No novel excipients are used in the formulation. The drug product specification includes tests for identification, assay, impurity, osmolality, viscosity, pH, particle size distribution, BAC, and sterility. The specification, as amended, is acceptable. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Batch analyses are provided for 3 batches of drug products in the commercial container closure system at $1/10^{th}$ commercial scales ((b) (4)). All batches complied with the proposed specification.

Twenty four months of stability data at long term condition (25°C/40%RH) and 6 months data at accelerated condition (40°C/25%RH) are provided for three commercial scale registration batches. Impurities including (b) (4) and individual impurities showed an increasing trend but remained within the proposed specification. These results which included statistical analysis supports both the expiration dating period and storage statement listed below.

1. **Strength:** Bromfenac ophthalmic solution, 0.075%
2. **Description/Commercial Image:** A sterile, preserved, (b) (4), viscous, multidose eye drop.
3. **Summary of Product Design:** Bromfenac ophthalmic solution
4. **List of Excipients:** See review notes, below
5. **Process Selection (Unit Operations Summary)**
    a. **Sterilization processes of the drug product, as applicable:** The Division of Microbiology Assessment has reviewed the sterilization processes used in the commercial production of the subject, sterile drug product. This submission is recommended for approval on the basis of sterility assurance.
    b. **Critical equipment:** None
6. **Container Closure:** 7.5 mL white low density polyethylene (LDPE) bottles (5 mL fill) with clear LDPE dropper tips, gray high density polyethylene (HDPE) dropper caps and white LDPE tamper-evident overseal. Each bottle is enclosed in a (b) (4) sealed laminated (b) (4) foil pouch.
7. **Expiration Date & Storage Conditions:** (b) (4) months with the storage statement of stored 15°C – 25°C (59° F – 77°F).
8. **List of co-packaged components:** None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	BromSite
Non Proprietary Name of the Drug Product	Bromfenac ophthalmic solution
Non Proprietary Name of the Drug Substance	Bromfenac
Proposed Indication(s) including Intended Patient Population	Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery
Duration of Treatment	1 day prior to surgery, the day of surgery, and 14 days post-surgery
Maximum Daily Dose	1 drop, twice/daily
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

ISV-303 is an ophthalmic solution of 0.075% bromfenac, a nonsteroidal anti-inflammatory drug (NSAID), for topical administration. The formulation used in the Phase 3 clinical trials is the same as the proposed commercial formulation. Since the Applicant has determined the plasma levels of the proposed drug, no biowaiver request has been submitted nor is it required. The pharmacokinetic (PK) study has been be reviewed by the Office of Clinical Pharmacology [OCP].
From the Biopharmaceutics perspective, NDA 206911 for bromfenac ophthalmic solution, 0.075%, is recommended for **APPROVAL.**

E. Novel Approaches None

F. Any Special Product Quality Labeling Recommendations None

G. Life Cycle Knowledge Information

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	• Formulation • Container closure[1] • Process parameters • Scale/equipment • Site[3]	H	Formulation includes a preservative; sterilization has been validated; facilities were recommended "Approval".	L	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	This is a topical product and therefore does not require testing for endotoxin.	L	No endotoxin testing required.

Antimicrobial Effectiveness of the Preservative	• Formulation	M	The formulation includes a preservative; initial antimicrobial effectiveness testing (AET) was adequate.	L	Post-approval stability protocol[2] will include AET.
Assay (API), stability	• Formulation • Container closure[1] • Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay (preservative)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	Analytical method adequately validated; stability data shows no trend and levels remain within the proposed specification.	L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	Fill volume (5 mL) is for the intended 16-day treatment; foiled pouch to (b) (4); drop size study and the minimal weight loss observed support deliverable volume.	L	Any changes to the (b) (4) and/or the (b) (4) process could affect weight loss.
Osmolality	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L	(b) (4) Clinically relevant specification; stability studies show no significant change.	L	
pH	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	(b) (4) formulation; No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>.	L	

[1] Stability studies demonstrate container closure compatibility with the drug product for all quality attributes

[2] Post-approval stability protocol provides for testing of all quality attributes

[3] Facilities have been recommended "Approval" indicating compliance with GMP

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

This NDA is recommended for approval from the Product Quality perspective.

Chunchun Zhang -S

Chunchun Zhang, Ph.D.; CMC reviewer; Branch 3; Division of New Drug Products I

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

The Applicant submitted this NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.50.

Currently, there are three FDA-approved bromfenac-containing ophthalmic products for the treatment of inflammation and pain post cataract surgery, including Xibrom (bromfenac 0.09%; BID; NDA 21664), Bromday (bromfenac 0.09%; QD; NDA 21664/SE2-013), and Proclensa (bromfenac 0.07%; QD; NDA 203168).

ISV-303 is a topical ophthalmic solution of 0.075% bromfenac, a nonsteroidal anti-inflammatory drug (NSAID), formulated in DuraSite®, InSite Vision's drug delivery system (b) (4) It is a sterile preserved, multidose eye drop intended for the treatment of post surgical inflammation and prevention of ocular pain in patients (b) (4) cataract (b) (4) surgery. ISV-303 is administered twice a day for 16 days – the day before surgery, the day of surgery and 14 days after cataract surgery.

ISV-303 is formulated with the drug substance bromfenac sodium sesquihydrate (equivalent to 0.075% bromfenac free acid) in the DuraSite delivery vehicle and other excipients. The Applicant stated that DuraSite as an ocular retention system for topical drug delivery to the eye. The DuraSite vehicle is comprised of (b) (4). DuraSite is a viscous polymeric suspension that adheres to the mucin covered layers of the eye surface. The polymer (b) (4) itself is an inert material, which does not penetrate eye tissues (b) (4) and is excreted via the nasolacrimal duct into the digestive tract. (b) (4) ISV-303 has target parameters for pH and osmolality of 8.3 and 290 mOsm/kg, respectively.

The Applicant also stated that the optimal pH for bromfenac stability in solution is centered near pH (b) (4), but the pH of ISV-303 is targeted to a lower range, 8.3 (b) (4) to ensure that the formulation has acceptable tolerability upon administration to the eye. Solubility of bromfenac in this pH range is well above the target concentration of ISV-303.

ISV-303 is formulated to a target osmolality of 290 ± 20 mOsm/kg, close to that of tear fluid (300 mOsm/kg). (b) (4)

ISV-303 is a viscous solution formulation with a viscosity of about (b) (4). The high viscosity of ISV-303 is attributed to (b) (4)

38. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?**

N/A. ISV-303 is a topical ophthalmic solution; therefore in vitro dissolution testing is not applicable.

39. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

The formulation used in the Phase 3 clinical trials is the same as the proposed commercial formulation presented below in Table 39.1.

Table 39.1 Formulation composition of ISV-303 for clinical, registration, and commercial batches

Development Use	Phase 1/2	Phase 2	Phase 3		Registration	Commercial
Clinical Study Number	C-10-303-001	C-11-303-002	C-11-303-003	C-12-303-004	-	-
Lot Number Manufacturer	F03W InSite Vision	E04X InSite Vision	01512B	00313B	00313B, 00313C, 00313D	TBD (b) (4)
Batch Size (kg)	(b) (4)					
API Source	(b) (4)					
Formula Control Number	303P10075A1		303P20075D1			
Ingredient	Concentration (% w/w)		Concentration (% w/w)			
Bromfenac Sodium Sesquihydrate	0.075[a]		0.075[a]			
(b) (4)						
Boric Acid, NF	(b) (4)					
Sodium Borate, NF						
Citric Acid Anhydrous, USP						
Sodium Citrate Dihydrate, USP						
Poloxamer 407, NF						
Benzalkonium Chloride, NF						
Polycarbophil, USP						
Sodium Chloride, USP						
Edetate Disodium Dihydrate, USP						
(b Sodium Hydroxide, NF	Adjust to pH 8.3		Adjust to pH 8.3			
(b) (4)						
Water For Injection, USP	-		(b) (4)			

[a]Expressed as free acid. TBD: To be determined.

The Applicant reported that the systemic exposure to bromfenac was assessed in a subgroup of patients enrolled in Study C-12-303-004 [phase 3 study] following topical ocular BID dosing of ISV-303. The Applicant concluded that the maximum plasma concentration of bromfenac at Day 1 was 2.42 ng/mL, and

after 16 days of dosing, 1.66 ng/mL, indicating a lack of systemic accumulation. These results confirm that systemic exposure of bromfenac is negligible after 16 days of BID ocular ISV-303 dosing.
In the Office of Clinical Pharmacology [OCP] Review[1], the OCP Reviewer concluded that following bilateral topical ocular twice-daily dosing [Study C-12-303-004] of ISV-303 ophthalmic solution, the plasma concentrations of bromfenac ranged from below the limit of quantification (LOQ = 0.20 ng/mL) to 2.42 ng/mL at 30 to 60 minutes post-dose.

Since the Applicant has determined the plasma levels of the proposed drug, no biowaiver request has been submitted nor is it required.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From the Biopharmaceutics perspective, NDA 206911 for bromfenac ophthalmic solution, 0.075%, is recommended for **APPROVAL.**

02/12/2016

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Concurrence and Signature:

I concur with Dr. Anand's assessment and recommendation.

2/17/2016

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products, OPQ.

[1] DARRTS: NDA-206911: REV-CLINPHARM-21(Primary Review): ZHANG, YONGHENG: 02/09/2016

ASSESSMENT OF MICROBIOLOGY

1. Are the tests and proposed release acceptance criteria for sterility and endotoxins limit adequate for assuring the microbial quality of the drug product?

Control of Drug Product
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.

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:
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.

- **Stability**
  Stability Summary and Conclusion

The proposed expiration date is [redacted] (b) (4) (b) (4)

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.

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.

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:

a. *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.*
b. *Provide AET results from product lots that are currently in the stability program.*
c. *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 the [redacted] (b) (4) proposed expiry [redacted] (b) (4) 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.

Reviewer's Assessment: Adequate
The applicant has provided successful results verifying release and stability sterility testing per USP<71>. AET (per USP<51>) will be performed routinely for post-approval

stability testing due to AET failures of multiple dose topical ophthalmic products preserved with benzalkonium chloride.

2.3.P.7 Container/Closure System

2. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

- Description of container closure system – The bottles [7.5 mL low density polyethylene (LDPE) bottles (5 mL fill volume)] are formed using (b) (4) (b) (4) (b) (4) The (b) (4) for the bottles is manufactured by (b) (4). The bottles and tips are manufactured by (b) (4), while the caps are manufactured by (b) (4)

- 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 x 107 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.

Information request sent on 18 September 2015:
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.

Reviewer's Assessment: **Adequate**
The applicant has provided sufficient results demonstrating the integrity of the container-closure as a microbial barrier.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

3. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: N/A

Reviewer's Assessment:
None of the materials used for the manufacture of the drug product are of biological origin or derived from biological sources.

4. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N/A

Reviewer's Assessment:
See Reviewer's Assessment for Question 42.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

QUALITY ASSESSMENT

The Division of Microbiology Assessment has reviewed NDA 206911 for BromSite™ (Bromfenac Ophthalmic Solution, 0.075% w/w), and found the microbiology information adequate. From a microbiology perspective, NDA 206911 is recommended for **APPROVAL.**

Jonathan G. Swoboda, PhD
Microbiology Reviewer
OPQ/OPF/Division of Microbiology Assessment Branch 3

Secondary Review Comments and Concurrence:
I concur with the microbiology assessment. NDA 206911 is recommended for **APPROVAL.**

John W. Metcalfe, PhD
Quality Assessment Lead (Acting)
OPQ/OPF/Division of Microbiology Assessment Branch 3

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

5. Is the applicant's claim for categorical exclusion acceptable?

6. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Reviewer's Assessment:

The applicant requests a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(b) on the grounds that the concentration of Bromfenac in the aquatic environment is expected to be less than 1 part per billion.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Adequate.
The claim is reasonable and should be acceptable.
Chunchun Zhang, Ph.D.; Review Chemist; Branch 3; Division of New Drug Product I.
Feb 27, 2016.

Secondary Review Comments and Concurrence:

I concur Feb 27, 2016.

Balajee Shanmugam, Ph. D.; Acting Branch Chief; Branch 3; Division of New Drug Product I.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

BromSite (bromfenac ophthalmic solution) 0.075%

-----DOSAGE FORMS AND STRENGTHS-----
Topical ophthalmic solution: bromfenac 0.075%.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name		Adequate
Dosage form, route of administration		Adequate
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		Adequate

Conclusion: Adequate.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

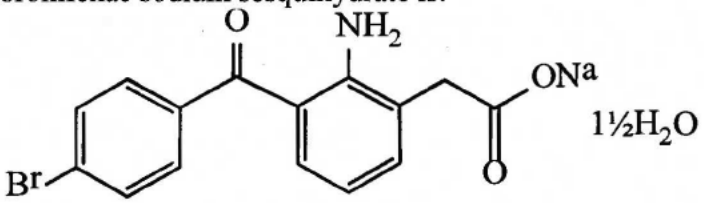
3 DOSAGE FORM AND STRENGTHS
Topical ophthalmic solution: bromfenac 0.075%.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		Adequate
Strengths: in metric system		Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Adequate

Conclusion: Adequate.

#11: Description (21CFR 201.57(c)(12))

BromSite (bromfenac ophthalmic solution) 0.075% is a sterile aqueous, topical NSAID, formulated in DuraSite®. The USAN name for bromfenac sodium sesquihydrate is bromfenac sodium. Bromfenac sodium is designated chemically as sodium [2-amino-3-(4-bromobenzoyl) phenyl] acetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2}H_2O$. The structural formula for bromfenac sodium sesquihydrate is:



Bromfenac sodium is a bright orange to yellow powder. The molecular weight of bromfenac sodium sesquihydrate is 383.17. BromSite is a greenish-yellow to dark yellow viscous liquid with an osmolality of approximately 290 mOsmol/kg.

Active: Each mL contains bromfenac sodium sesquihydrate 0.81 mg, which is equivalent to bromfenac free acid 0.76 mg.

Preservative: benzalkonium chloride 0.005%

Inactives: boric acid, sodium borate, citric acid anhydrous, sodium citrate dihydrate, poloxamer 407, polycarbophil, sodium chloride, edetate disodium dihydrate, sodium hydroxide (to adjust pH to 8.3), and water for injection (USP).

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Adequate
Dosage form and route of administration		Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)		Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		Adequate
Statement of being sterile (if applicable)		Adequate
Pharmacological/ therapeutic class		NA
Chemical name, structural formula, molecular weight		Adequate
If radioactive, statement of important nuclear characteristics.		NA
Other important chemical or physical properties (such as pKa, solubility, or pH)		NA

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

BromSite (bromfenac ophthalmic solution) 0.075% is supplied in white opaque low density polyethylene (LDPE) plastic bottles and translucent dropper tips, and gray high density polyethylene (HDPE) eyedropper caps. A white tamper evident overcap is provided. Each bottle is provided in a sealed foil laminated pouch.

5 mL in a 7.5 mL bottle (b) (4)
(NDC No. 58104-303-50)

STORAGE

Store at 15°C – 25°C (59° F – 77°F). Discard after treatment completion.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate
Special handling (e.g., protect from light, do not freeze)		NA
Storage conditions		Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		Adequate

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

[redacted]

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration 21.CFR 201.100(b)(3))		Not available
Net contents* (21 CFR 201.51(a))		Not available
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		Not available
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)		Not available
Storage (not required)		NA
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate
Others		NA

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: There is some information missing such as route of administration, net content and inactive ingredients on the intermediate container. It is acceptable because of the space and is included in the PI.

2) Carton Labeling

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		Adequate
Sterility Information (if applicable)		Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)		Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)		NA
Route of Administration (not		Adequate

required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.
Include an equivalency statement to indicate the amount of active moiety related to the amount of active ingredient (salt). This equivalency statement should appear on the container label, carton labeling, and other labeling.
"*"Each mL of BromSite ophthalmic solution contains:*
***Active**: bromfenac sodium sesquihydrate 0.81 mg equivalent to bromfenac free acid 0.76 mg."*

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

All product quality labeling comments are marked up and will be finalized during team labeling review.
Chunchun Zhang, Ph.D.; Reviewer Chemist; Branch 3; Division of New Drug Products I.
Feb 27, 2016.

Secondary Review Comments and Concurrence:

I concur Feb 27, 2016.

Balajee Shanmugam, Ph. D.; Acting Branch Chief; Branch 3; Division of New Drug Product I.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 206911	**Submission Type: 505(B)(2)**	**Established/Proper Name: ISV-303**
Applicant: InSite Vision Inc.	**Letter Date: June 10, 2015**	**Dosage Form: Ophthalmic Solution**
Chemical Type:	**Stamp Date: June 10, 2015**	**Strength: 0.075% w/w**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			NA

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☒	☐	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other _____	☐	☒	

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FILING REVIEW

Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☐	☒	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other_____		☐	☒	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	☒	
36.		Excipients	☐	☒	
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☐	☐	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	N/A. The formulation is an ophthalmic solution.
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	No bioequivalence study submitted
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☒	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices	☒	☐	☐	

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C. FILING CONSIDERATIONS					
	○ Facilities and Equipment ○ Adventitious Agents Safety Evaluation ○ Novel Excipients ❑ Regional Information ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols				
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☐	☐	☒	
	DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be	☒	☐	☐	The drug substance DMF may have some deficiencies.

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C. FILING CONSIDERATIONS					
	licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using	☒	☐	☐	

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C. FILING CONSIDERATIONS					
	the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	No bioequivalence study submitted (two Phase 3 efficacy studies have been submitted)
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	The formulation used in the Phase 3 efficacy studies is same as the Registration, and Commercial Lots (Table 2.3.P.2-1)
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	☒	No biowaiver request
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	NA, It is an ophthalmic solution formulation (immediate release).
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	5 FOR MC	☐	☒	NA, It is an ophthalmic solution formulation (immediate release).

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C. FILING CONSIDERATIONS					
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	There is no claim for BCS I designation in this application.
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			☒	

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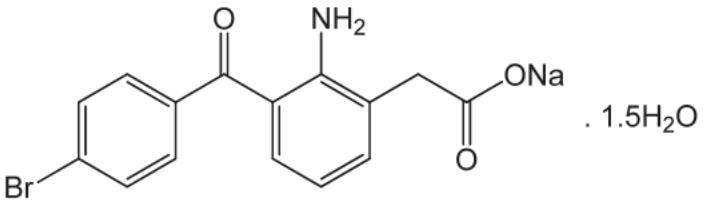
FILING REVIEW

This DP is sterile multidose topical ophthalmic solution for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing ocular surgery. Dose 2X for 16 days. In the DP spec, the appearance is listed as "Greenish yellow to yellow, [redacted] liquid." I am not sure we could still call it a "solution."



Bromfenac sodium
sodium 2-(2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate
Chemical Formula: $C_{15}H_{14}BrNNaO_{4.5}$
Molecular Weight: 383.17

Drug Substance:

The API has been used in other FDA approved products (Xibrom: withdrawn from market for business reason, Bromday, Prolensa). The applicant has referred to the DMF [redacted] for the API. This DMF has NEVER been reviewed, but was reviewed for completeness by the OGD. The DS spec looks reasonable.

Bromfenac Sodium Sesquihydrate Drug Substance Supplied by [redacted]

Test	Test Method	Acceptance Criteria
Appearance	TM224	Bright orange to yellow powder
Identification by IR	USP <197K>	Pass
Identification by HPLC retention	TM057	Pass
Identification sodium [redacted]	USP <191>	Pass
pH	TM226	[redacted]
Water	USP <921>	[redacted]%
Heavy Metals	USP <231> Method II	NMT [redacted]ppm
Assay [redacted]	TM057	[redacted]%
Related Substances	TM057	Impurity [redacted] NMT [redacted]% Impurity [redacted] NMT [redacted]% Single impurity NMT [redacted]% Total impurities NMT [redacted]%
Residual Solvents	Acceptance is based on manufacturer's Certificate of Analysis	[redacted] NMT [redacted] ppm (ICH Class 2) [redacted] NMT [redacted] ppm [redacted] NMT [redacted] ppm (non ICH) [redacted] NMT [redacted] ppm [redacted] NMT [redacted] ppm (ICH Class 2) [redacted] NMT [redacted] ppm (ICH Class 2) [redacted] NMT [redacted] ppm (ICH Class 2)

		(b) (4) NMT (b) (4) ppm (ICH Class 2) (b) (4) NMT (b) (4) ppm
(b) (4)	Acceptance is based on manufacturer's Certificate of Analysis	NMT (b) (4) µg/g

NMT = Not more than

(b) (4)

Drug Product:

All the DP manufacturing sites are in the US. A description of the manufacturing process for the (b) (4) commercial scale is provided. The DP formulation along with roles of each ingredient is provided (benzalkonium chloride is used as antimicrobial preservative, EDTA disodium (b) (4)). All the excipients are compendial grade. The process flow diagram is provided in Section 3.2.P.3.3.

Drug Product Formulation

Ingredient	% W/W	Weight In 500 kg Batch (Grams)
Bromfenac Sodium Sesquihydrate	(b) (4)	
Boric Acid, NF		
Sodium Borate, NF		
Citric Acid, Anhydrous, USP		
Sodium Citrate Dihydrate, USP		
Poloxamer 407, NF		
Benzalkonium Chloride [d], NF		
Polycarbophil, USP		
Sodium Chloride, USP		
Edetate Disodium Dihydrate, USP		
(b) (4) Sodium Hydroxide, NF	Adjust to pH 8.3	(b) (4)
Water for Injection, USP	(b) (4)	

[a] Bromfenac free acid equivalent
[b] Bromfenac sodium equivalent
[c] Adjusted for potency
[d] Benzalkonium chloride (b) (4)

The DP spec looks reasonable, though the pH is on the higher side (b) (4). Some of the degradant specs for stability looks on the higher side though daily exposure for a 0.075% solution might still be very low. The applicant provided batch data for two registration batches and one "Phase 3 and registration batch." Batch data for three more phase1, 2, and 3 batches are included. The primary cc includes a

bottle (manufactured by (b) (4)), a dropper tip, and a cap for closure. The bottle has 7.5 mL capacity with a fill volume of 5 mL fill.

Proposed Drug Product Specification (Release)

Attribute	Method	Acceptance Criterion
Identification (Bromfenac) HPLC Retention Time	TM058	Pass
Identification (Bromfenac) UV/Vis	TM058	Pass
Bromfenac Content	TM058	(b) (4)% (b) (4)% of label)
Chromatographic Purity	TM058	RRT (b) (4) NMT (b) (4)% RRT NMT (b) (4)% Unspecified NMT (b) (4)% Total impurities NMT (b) (4)%
Appearance	TM423	Greenish-yellow to yellow, (b) (4) (b) (4) liquid
pH	TM601	(b) (4)
Osmolality	TM414	(b) (4) mOsm/Kg
Viscosity	TM424	(b) (4) cps
Benzalkonium Chloride	TM055	(b) (4)%
Particulates	TM425	NMT (b) (4) NMT NMT
Sterility	TM800	Sterile

NMT = not more than

Three registration batches two with 2.5 mL fill and one with 5 mL provided at 25C/40%RH (12 months) and 40C/25%RH conditions (6 months). Simulated use, shipping, and freeze-Thaw results also provided. Labeling info provided.

Initial Risk Assessment:

Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Non-sterile unit(s)	4	5	5	100		H
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Excessive endotoxin level	2	4	4	32		M
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters	• Impurity formation due to excipient reactions or unspecified	3 (Mod stable	2	1	6	Moderately Stable Drug: No single impurity > (b) (4)%;	L

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FILING REVIEW

Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
	• Scale/equipment • Site	reactions • Hydrolytic degradation (moisture) • Organic solvents	drug)				Total impurities < (b) (4) % w DMF	
Assay (preservative)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Lack of effectiveness through shelf-life	1 (Release) 1 (Stability)	1	1	1	Preservative used: 0.005% benzalkonium chloride (Assay monitored in Specs at release and stability). Multidose.	L
Assay (anti-oxidant)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Decrease in potency					Not used	L
Uniformity of Dose (Fill Volume/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Insufficient dose	4	3	4	48	Not enough information. Not in release or stability specifications. Scale up issues. Process homogeneity issues. Lack of process development data. Lack of in-process controls.	M
Osmolality	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Irritation • Edema	2	2	2	8	Osmolality testing is performed (DP specifications).	M
pH-	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Irritation • Particulate formation due to delamination (with high pH) • API degradation	4	4	3	48	Testing is performed (DP specifications). Process homogeneity issues. API stability issues. Lack of process development data. Lack of in-process controls.	L

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Irritation • Embolism	3	5	2	30	Tested in DP specifications.	M
Leachable extractables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Generation of impurities	4	4	3	48	Test data provided	M
Appearance (Color/turbidity)	• Formulation • Container closure • Process parameters • Scale/equipment • Site		3	3	1	9		L

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2015.08.07 14:53:26 -04'00'