CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

CHEMISTRY REVIEW(S)

To: NDA 203168 File

Date: O5-April-2013

From: Rapti D. Madurawe, Ph.D., Branch Chief, Branch V/Division II, ONDQA

Dr. Rao Kambhampati recommended CMC labeling revisions in Addendum1 to Review #1 dated 04-April-2013. The recommended labeling changes may be made post-approval and the NDA may be approved with the current labeling provided in Amendment 0012 dated 03-April-2013.

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/s/

RAPTI D MADURAWE
04/05/2013

NDA# 203168
Addendum 1 to Quality Review #1
For Division of Topical and Ophthalmology Products

1. NDA# **203168**

2. Amendment # and Date: 0011 dated 3/18/13

3. REVIEW DATE: 4-4-13

4. REVIEWER: Rao V. Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N203168 ORIG-1 0000 (0) Quality Review	2/25/13

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Global Submit Date
NDA 203-168 Amendment 0011 (11)	3/18/13

7. NAME & ADDRESS OF APPLICANT:

Name:	Bausch & Lomb Incorporated (formerly ISTA Pharmaceuticals, Inc.)
Address:	50 Technology Drive Irvine, CA 92618
Representative:	N/A
Telephone:	949-727-0833

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Prolensa™
b) Non-Proprietary Name (USAN): Bromfenac ophthalmic solution, 0.07%
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA (CDA, 21 CFR 314.50), 505 (b)(1)

10. PHARMACOL CATEGORY: Nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use (Cyclooxygenase 1 and 2 inhibitor)

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 0.07%

13. ROUTE OF ADMINISTRATION: Topical (ocular) instillation

14. Rx/OTC DISPENSED: _X__Rx ___OTC

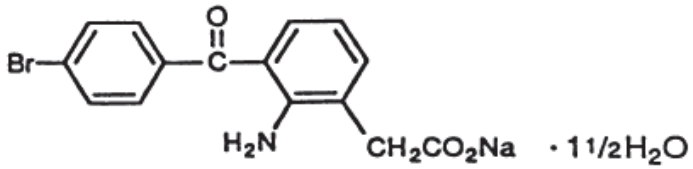
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Sodium [2-amino-3-(4-bromobenzoyl) phenyl] acetate sesquihydrate
or
Benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate



$C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2} H_2O$
383.17
USAN Name: Bromfenac sodium

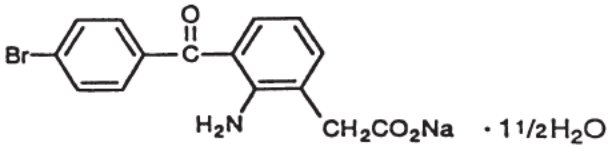
Review

The Quality (CMC) review of this NDA# 203-168 was filed in DARRTS on 2/26/13. On 3/18/13, the applicant submitted an amendment #0011 (11) in response to the DTOP's e-mail communication dated 3/15/13 regarding labeling and labels. This addendum includes the quality review of the amendment #11.

Package Insert: *The changes below (indicated in red) are recommended to the draft package insert that was submitted in amendment #11. The recommended changes show the active as a sesquihydrate* [redacted] (b) (4)

11 DESCRIPTION

PROLENSA (bromfenac ophthalmic solution) 0.07% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of PROLENSA contains 0.805 mg bromfenac sodium sesquihydrate (equivalent to 0.7 mg bromfenac free acid). Bromfenac sodium is designated chemically as sodium [2-amino-3-(4-bromobenzoyl) phenyl] acetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \bullet 1\frac{1}{2}H_2O$. The chemical structure for bromfenac sodium [redacted] (b) (4) is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. PROLENSA ophthalmic solution is supplied as a sterile aqueous 0.07% solution, with a pH of 7.8. The osmolality of PROLENSA ophthalmic solution is approximately 300 mOsmol/kg.

Each mL of PROLENSA ophthalmic solution contains:

Active: bromfenac sodium [redacted] (b) (4) sesquihydrate [redacted] (b) (4) which is equivalent to [redacted] (b) (4) bromfenac free acid.

Preservative: benzalkonium chloride [redacted] (b) (4) 0.005% [redacted]

Inactives: boric acid, edetate disodium, povidone, sodium borate, sodium sulfite, tyloxapol, sodium hydroxide to adjust pH and water for injection, USP.

Container and Carton Labels: The applicant submitted the following revised labels for the packaging configurations indicated in the Table 1 below:

Table 1. Draft Labeling Components for PROLENSA™ (bromfenac ophthalmic solution) 0.07%

Configuration	Draft Component
0.6 mL Professional Sample NDC No. 24208-601-06	0.6 mL Sample Bottle Label
	0.6 mL Sample Carton
0.8 mL Professional Sample NDC No. 24208-601-08	0.8 mL Sample Bottle Label
	0.8 mL Sample Carton
1.6 mL Trade NDC No. 24208-601-01	1.6 mL Sample Bottle Label
	1.6 mL Sample Carton
3 mL Trade NDC No. 24208-601-03	3 mL Sample Bottle Label
	3 mL Sample Carton

(b) (4)

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

(b) (4)

Comments*: The above revised draft labels contain all the required CMC related information except the carton labels do not contain equivalency statement for the active ingredient. Presently, the statement reads as follows:* "Each mL of Prolensa ophthalmic solution contains: **Active**: bromfenac sodium hydrate 0.805 mg". **Preservative**: benzalkonium chloride (0.005%) …….. *In this statement active is given in mg, active name includes "hydrate", no equivalency statement, and benzalkonium chloride is given in %. Preservative is identified separately.*

To a related NDA# 21-664 (Xibrom™), the same applicant (ISTA was acquired by Bausch & Lomb) submitted (b) (4) *:*

(b) (4)

For NDA 203-168 Carton Labels: *"Each mL of Prolensa™ ophthalmic solution contains:*

(b) (4)

Conclusion and Recommendation: *We recommend the above changes to the draft package insert and carton labels.*

Primary Reviewer: Rao V. Kambhampati, Ph.D.

Secondary Reviewer: Rapti Madurawe, Ph.D.

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/s/

RAO V KAMBHAMPATI
04/04/2013

RAPTI D MADURAWE
04/04/2013

NDA 203168

Prolensa™ (bromfenac ophthalmic solution) 0.07%

Applicant: ISTA Pharmaceuticals, Inc.

Quality (CMC) Review #1

Rao V. Kambhampati, Ph.D.

For Division of Transplant and Ophthalmology Products (DTOP)

Table of Contents

Chemistry Review Data Sheet

1. NDA# **203168**

2. REVIEW #: 1

3. REVIEW DATE: 2-25-13

4. REVIEWER: Rao V. Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Global Submit Date
N203168 ORIG-1 0000 (0)	6/7/2012
Amendment 0001 (1)	8/21/12
Amendment 0002 (2)	8/31/12
Amendment 007 (7)	11/19/12
Amendment 008 (8)	12/19/12
Amendment 009 (9)	12/21/12

M. NAME & ADDRESS OF APPLICANT:

Name:	Bausch & Lomb Incorporated (formerly ISTA Pharmaceuticals, Inc.)
Address:	50 Technology Drive Irvine, CA 92618
Representative:	N/A
Telephone:	949-727-0833

M. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet NDA 203168

a) Proprietary Name: Prolensa™
b) Non-Proprietary Name (USAN): Bromfenac ophthalmic solution, 0.07%
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA (CDA, 21 CFR 314.50), 505 (b)(1)

10. PHARMACOL CATEGORY: Nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use (Cyclooxygenase 1 and 2 inhibitor)

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 0.07%

13. ROUTE OF ADMINISTRATION: Topical (ocular) instillation

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
2-Amino-3-benzoylbenzeneacetamide
or
2-(2-Amino-3-benzoylphenyl)acetamide

$C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2} H_2O$
383.17

17. RELATED/SUPPORTING DOCUMENTS:

M. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
016414	II	Senju Pharmaceutic	Bromfenac sodium	1	Adequate	10/26/04 and 2/20/13

		al Co., Ltd.	(Produced by Regis Technologies, Inc.)			
(b) (4)	III	(b) (4)		1	Adequate	11/26/12
	III			1	Adequate	10/24/12
	III			1	Adequate	12/19/12
	III			1	Adequate	11/14/12
	III			1	Adequate	1/26/07
	III			1	Adequate	11/14/12
	III			1	Adequate	8/31/07

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	020535	Duract® (bromfenac sodium), Pfizer Inc., agent for Wyeth Pharmaceuticals
IND	060295	ISTA Pharmaceuticals, Inc., Bromfenac (Sodium) Ophthalmic Solution(s)
NDA	021664	ISTA Pharmaceuticals, Inc., Bromfenac Ophthalmic Solution 0.09%, Approved

M. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	7/27/12	A. Alexandrow (HFD-001)
LNC (ONDQA)	Not applicable	2/20/13	Rao Kambhampati, Ph.D.
Methods Validation	Not applicable	2/20/13	Rao Kambhampati, Ph.D.
OMEPR	Proprietary name acceptable (review in DARRTS)	11/7/12	Jung Lee, RPh.
EA	Acceptable	1/30/13	Rao Kambhampati, PhD
Product Quality Microbiology	Acceptable	1/22/13	Stephene E. Langille, Ph.D.

19. ORDER OF REVIEW (OGD Only): N/A

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 203168

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate CMC information as required. The tradename, Prolensa™, for the drug product is acceptable. The establishment evaluation of the manufacturing and testing facilities was complete and the Office of Compliance issued an Overall Acceptable Recommendation for this NDA. From the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

The Active Pharmaceutical Ingredient (API) in the drug product is bromfenac sodium drug substance. The same drug substance is used in the manufacture of the currently marketed bromfenac ophthalmic solution 0.09% formulation in this applicant's original NDA 21-664, which was approved on 24 March 2005. The manufacturer and supplier, manufacturing process, test methods, specifications, and all other parameters are the same as those applied to the drug substance for the currently approved Xibrom™/Bromday™ 0.09% formulation. Bausch & Lomb (formerly ISTA Pharmaceuticals®, Inc.; ISTA) makes reference to Senju's Type II Drug Master File (DMF) 16414 for pertinent information required for drug substance and a Letter of Authorization was provided from Senju. The original DMF was reviewed by Yong-de Lu (ONDQA) on 10/16/04, who found it to be adequate and the subsequent Annual Reports (1 to 10) were reviewed by this reviewer. The DMF is again found to be adequate and a Chemistry Review #2 (February 2013) was filed in DARRTS.

Drug Product:

The drug product is a non-steroidal anti-inflammatory drug (NSAID) for topical ophthalmic use. It is supplied as a clear, yellow, sterile solution containing 0.07% bromfenac free acid and dispensed from a 7.5cc capacity white low density polyethylene (LDPE) bottle with a white linear (b) (4) tip, and grey (b) (4) screw cap. The proposed trade sizes for the drug product are 1.6 mL and 3 mL per bottle. In addition, the applicant proposed sample sizes of 0.6 mL and 0.8 mL per bottle.

Each 1 mL of the drug product contains 0.085 mg of bromfenac sodium sesquihydrate (equivalent to 0.07% of free acid form) as the active ingredient and the following excipients: boric acid (b) (4) and sodium borate (b) (4) sodium sulfite (b) (4) tyloxapol (b) (4) and povidone (b) (4) edetate disodium (b) (4) benzalkonium chloride (b) (4) as preservative; and sodium hydroxide (if necessary to adjust pH to 7.8).

The components of the container closure system used for bromfenac ophthalmic solution 0.07% are identical to the marketed bromfenac ophthalmic solution 0.09%. Bromfenac ophthalmic solution, 0.07% is (b) (4) filled into 7.5 cc size (b) (4) (b) (4) low-density polyethylene (LDPE) white (b) (4) round bottles into which a (b) (4) controlled dropper tip is then inserted. The bottle is sealed by application of a (b) (4) screw-on gray (b) (4) cap. A tamper-evident (b) (4) seal is shrink-sealed over the cap and the neck of the bottle.

The drug product is manufactured by Bausch & Lomb Pharmaceuticals, Inc. (B&L) in Tampa, FL. The manufacturing process involves the following important steps: (b) (4)

The revised specification for the drug product included appearance of solution, description of container, identification (UV and HPLC), bromfenac sodium assay (HPLC; 90-110%), bromfenac impurities (total), (b) (4) any individual specified impurity (excluding (b) (4)), any individual unspecified impurity, pH, osmolality, benzalkonium chloride, EDTA, sodium sulfite, sterility, bacterial endotoxins, particulate matter, weight loss. In the initial specification, the applicant did not include tests for sodium sulfite and weight loss.

B&L tests the incoming raw materials and, produces and tests the final product (release and ongoing stability). Container closure system was tested per USP <661> and <87>. In addition, drug product filled container closure systems were tested for leachable/extractable levels and studies are ongoing through end of shelf life. A safety

evaluation of these potential substances indicates the levels are below their safety threshold. The container closure system (bottle, dropper tip and cap) components are [redacted] (b) (4) The container-closure system was shown to maintain the sterility of the finished product. Studies showed that the finished product is not adversely affected by light exposure or extreme temperatures.

Bromfenac ophthalmic solution, 0.07% utilizes an [redacted] (b) (4) The manufacturing process validation will be completed prior to commercialization. B&L will perform process validation on 3 consecutive commercial scale batches of bromfenac ophthalmic solution, 0.07%.

Stability data are available for the 0.6 mL and 3 mL fill sizes. Although the stability of the 0.8 mL and 1.6 mL fill sizes were not directly investigated, these fill sizes are bracketed (based on ICH Q1D) between two extreme fill sizes. The 0.8 mL fill is bracketed between the studied 0.6 mL and 1 mL configurations while the 1.6 mL fill is bracketed by the studied 1.5 mL and 3 mL configurations. Consequently, the proposed expiry for the 0.8 mL and 1.6 mL fill sizes will default to the most conservative of the bracketed extremes, which are the 0.6 mL and 3 mL fills, respectively. Based on 12 months of real-time data, the expiration period granted is 12 months for the 0.8 and 0.6 mL fill sizes. Based on 18 months of real-time data, the expiration dating period granted is 22 months for the 1.6 and 3 mL fill sizes. The recommended label storage condition is 15°C-25°C (59°F-77°F).

B. Description of How the Drug Product is Intended to be Used

PROLENSA™ (bromfenac ophthalmic solution) 0.07% is supplied in a white LDPE plastic squeeze bottle with a 15 mm [redacted] (b) (4) white dropper-tip and 15 mm [redacted] (b) (4) gray cap as follows:

- 1.6mL in a 7.5mL container (NDC 24208-602-01)
- 3.0mL in a 7.5mL container (NDC 24208-602-03)

One drop of PROLENSA™ ophthalmic solution is applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

In addition, Prolensa is supplied in sample size bottles (7.5 mL) containing 0.6 mL or 0.8 mL solution.

C. Basis for Approvability or Not-Approval Recommendation

The applicant resolved all the CMC related deficiencies that were communicated in the 74-day and IR letter. The proposed formulation (0.07%) is a lower strength formulation of the currently approved formulation (0.09%) with some changes in the some of the excipients. The drug substance is manufactured and tested by the same facilities that are

used for approved formulation. The applicant demonstrated that the drug product can be manufactured with consistent quality and purity by providing adequate batch analysis and including controls in the manufacturing and packaging operations. The specification for drug substance and drug product included all the tests that are required for a topical ophthalmic solution. Adequate stability data were provided for the drug substance and drug product. The product quality microbiology of this NDA was reviewed by the Microbiology Staff (OPS) reviewer and it was found to be acceptable after addressing all the deficiencies in the NDA. All the facilities involved in the manufacturing, testing, and packaging of the drug substance and drug product were found to be acceptable and an Overall Acceptable Recommendation for this NDA was issued by the Office of Compliance. The established name need not be reviewed because it is already marketed with the same name. The tradename, Prolensa™, is acceptable from all the reviewers stand point as well as by the OMEPR (CDER).

III. Administrative

A. Reviewer's Signature

Rao V. Kambhampati, Ph.D.

B. Endorsement Block

Primary Reviewer/Date: Rao V. Kambhampati, Ph.D.
Secondary Reviewer/Date: Rapti Madurawe, Ph.D.

C. CC Block

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/s/

RAO V KAMBHAMPATI
02/26/2013

RAPTI D MADURAWE
02/26/2013

Initial Quality Assessment Branch V
Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products
NDA: 203-168
Applicant: ISTA
Stamp Date : 07 June, 2012
Proposed Trademark: Prolensa*
Established Name: Bromfenac ophthalmic solution 0.07%
Dosage Form: Ophthalmic solution
Route of Administration: Topical
Strength: 0.07%
Indication: Treatment of inflammation and pain associated with cataract extraction
Reviewer : Rao Kambhampati
Quality Micro Reviewer: Steven Langille
CMC Lead : Bala Shanmugam

	YES	NO
Acceptable for filing:	☒	☐
Comments for 74-Day Letter:	☒	☐

Summary and Critical Issues

Summary

Bromfenac ophthalmic solution 0.07% is administered once daily for the treatment of postoperative inflammation and reduction of ocular pain after cataract surgery. The NDA is filed as a 505 (b) (1). The submission is all electronic and located in the EDR (Link: \\CDSESUB1\EVSPROD\NDA203168\203168.enx)

ISTA, the sponsor of the NDA under review is currently marketing a similar product, Bromday™ (bromfenac ophthalmic solution), 0.09% which was approved in 2010 (sNDA 21664) which itself had a change in dosing regimen (QD) compared to the previously approved (March 2005) twice-a-day Xibrom™ product.

In addition to the change in the concentration of bromfenac sodium, the current formulation has been slightly modified as compared to the approved product in that it replaces (b) (4) with tyloxapol. Bausch and Lomb, the manufacturer of the approved product will also manufacture the new formulation. The drug substance manufacturer also remains to be the same (Regis Technologies).

* Based on initial evaluation, the proposed proprietary name was determined to be "conditionally acceptable" (Section 1.6.3, General Correspondence, Communication of May 14, 2012).

Chemistry information for the drug substance, bromfenac sodium is referenced to DMF 16414. A LOA from the DMF holder, Senju Pharmaceuticals is provided. Please note that Regis Technologies is the contract manufacturer of the drug substance.

The drug product is formulated as a sterile ophthalmic solution for topical administration and the proposed commercial trade sizes are 1.6 mL and 3.0 mL in 7.5 mL LDPE bottle. Additionally, physician sample size of 0.6 mL and/or 0.8 mL in 7.5 mL LDPE bottle is also being proposed. Please note that bracketing approach has been used to support stability of the different fill volumes. The company is requesting a shelf-life of 12-months for the physician sample sizes and 22-months for the 1.6 mL and 3.0 mL commercial sizes when stored at 15-25°C.

Manufacturing and testing facilities have been entered in EES.

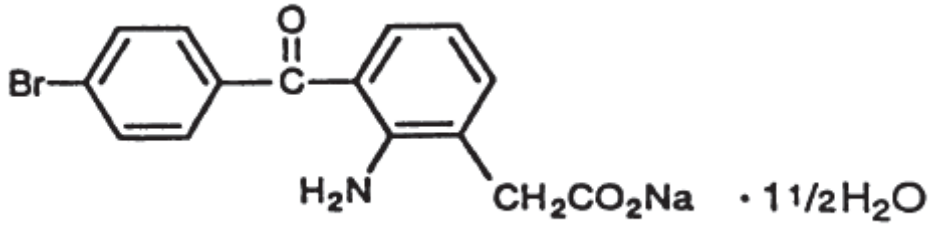
The IND related to this submission is IND 060295. Please note that a pre-NDA meeting was held. The minutes of the Pre-NDA meeting is attached to this IQA for immediate reference.

This NDA will be reviewed on a Standard time line.

Important Timelines:

- Primary reviews - March 3, 2013
- Proposed labeling to applicant- target date- March 10, 2013
- CDTL review- March 17, 2013
- Circulate action package- March 17, 2013
- PDUFA – April 7, 2013

Drug Substance



All drug substance information related to manufacturing (contract manufactured by Regis Technologies) and controls is referenced to DMF 16414 (see table for status of this DMF at the time of this IQA). A letter of authorization from the DMF holder, Senju Pharmaceuticals has been provided.

Drug Substance	DMF #	LOA provided (Yes/No)	Status	Comments
Bromfenac sodium	16414	Y	The last review is by Yong De Lu, dated October 26, 2004.	There are several Annual Reports to be reviewed.

- As indicated above, Regis Technologies, Morton Grove, IL is the contract manufacturer for Senju Pharmaceuticals.
- The sponsor also references NDA 21-664 (Wyeth) substance for the drug substance and has and provided a LOA from Pfizer (agent for Wyeth).
- Per company statement (Section 2.3.S.1), the manufacturing process, controls, specifications etc are the same as those for the drug substance for the currently approved.

Drug Product

The product is formulated as a sterile, preserved ophthalmic solution.

- The drug product is manufactured by Bausch and Lomb, Inc., Tampa FL.
- All excipients used in the formulation are compendial
- The drug product composition is attached to this review
- Manufacturing process involves (b) (4)
- (b) (4) *Whether adequate in-process tests are in place to ensure that product quality does not deteriorate during hold time should be verified.*
- Table 2 in Section 3.2.P.3.3 provides a summary of the batch lots used in clinical and stability for which executed batch records have been provided.
- The DP specification is attached for quick reference. The company has proposed separate release and regulatory specification with differences in acceptance criteria for pH, osmolality, benzalkonium chloride and EDTA. The acceptance limits for (b) (4) is set at NMT (b) (4) and total impurities at NMT (b) (4) *The impurities listed in Table 1, Section 3.2.P.5.1 does not list those specified in Table 4, Report S00156-R (Stability Report from Primary Stability Batches of Bromfenac Ophthalmic Solution 0.07%). Specifically, the above referenced report, the specification includes test and acceptance limit for* (b) (4) *at NMT* (b) (4) *The reporting of the impurities requires careful scrutiny and also consulted with Pharm/Tox on the qualification of the impurities. The proposed acceptance values for the aforementioned (specifically of* (b) (4)*) should be evaluated* and *tightened if needed based on batch and stability data. Additionally, the proposed impurities and the levels should be compared to the currently marketed approved product.*
- *The specification does not provide a test for residual solvents. It needs to be verified if potential residual solvents are controlled in the raw materials. The*

need for the company to provide a statement that the drug product complies with USP <467> can be determined during review.

- *While providing tests for sodium sulfite and weight loss (the later is proposed only for stability), the drug product specification does not provide acceptance criteria for both attributes. The company should propose appropriate acceptance limits for these quality attributes.*
- *As indicated earlier, bracketing approach has been used in supporting stability of the various fill sizes proposed. The proposed trade sizes are 1.6 mL and 3.0 mL and the proposed sample sizes are 0.6 mL and/or 0.8 mL. Stability studies have used 0.6 mL, 1.0 mL, 1.5 L, and 3.0 mL fill sizes which brackets the 0.8 ml sample size and the 1.6 mL trade size. What, if any, effects of the (different) headspace in the various packaging configurations have on the quality of the product over the shelf-life should be assessed.*
- *The trend in quality attributes on stability should be evaluated in considering the proposed shelf-life of 22-months and how it affects, if any the shelf-life attributes of the drug product. Any correlation between the observed trends may aid in the tightening of the specification and in determining the appropriate shelf-life. For example, is the observed trend in assay values influenced by the weight loss/gain? Among the quality attributes tested, the trends are prominent with osmolality, assay for sodium sulfite (note there is a significant drop in value in the initial stages) and weight loss irrespective of the orientation. The trends are even more pronounced under accelerated conditions. In addition to the effect on quality, the other question to consider is, how will the drug product, for marketing, be shipped and if transportation storage conditions will impact the quality of the product.*
- *The leachable study has identified several organic volatile and organic semi-volatile leachables peaks and several unidentified (see above referenced report). Two peaks tentatively identified as* [redacted] (b) (4) *and* [redacted] (b) (4) *and several other leachables were detected at levels above the identification and qualification threshold of > 1μg/g. Report S00245-R (Appendix 4) provides a safety evaluation of these compounds. Whether the origin of these leachables has been traced is unclear. Though a safety report has been provided, given the plethora of leachables, a toxicology consult should be considered to ensure that the levels of the various leachables pose no safety risk. Also, it should be determined during review if the leachable(s) should be included in the DP specification with appropriate acceptance limits.*
- The container closures are [redacted] (b) (4) *Whether residual levels of* [redacted] (b) (4) *and* [redacted] (b) (4) *are controlled should be checked.*
- The carton and container labels mentions "Sample-Not for sale". *Whether this is acceptable or should the label specifically state "Physician sample" may be discussed with Clinical/DMEPA.*
- *The NDA does not provide the color mock of the container and carton labels. This should be communicated in the 74-day letter to the company.*

Early action needed:

1) Reviewer should evaluate items identified (*in italics)* in this IQA.

Comments for 74-day letter

The following comments will be communicated to the company.

1. Please submit color mock of the carton and container labels
2. The drug product specification proposes a test for weight loss and sodium sulfite but does not provide for acceptance criterion. Please propose a suitable acceptance limit for this test.

Comments and Recommendation:

Based on the perusal of this NDA, it is determined to be complete and therefore filable from CMC perspective. Dr. Rao Kambhampati is assigned to review this NDA.

Balajee Shanmugam	*See DARRTS*
CMC Lead	Date
Rapti Madurawe, Ph.D.	*See DARRTS*
Branch Chief	Date

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: August 29, 2011, Start: 9:05, End: 9:25
Meeting Location: Bldg 22, Room 1313

Application Number: IND 60295
Product Name: Bromfenac ophthalmic solution, 0.07%
Indication: for treatment of inflammation and pain associated with cataract surgery

Sponsor/Applicant Name: ISTA Pharmaceuticals, Inc.

Meeting Chair: Renata Albrecht, M.D.
Meeting Recorder: Raphael R. Rodriguez

FDA ATTENDEES
Renata Albrecht, M.D. Director, DTOP
Wiley Chambers, M.D., Deputy Director, DTOP
David Roeder, Assoc. Director for Regulatory Affairs, OAP
William Boyd, M.D., Clinical Team Leader
Rhea Lloyd, Clinical Reviewer
Martin Nevitt, M.D., Clinical Reviewer
Jennifer Harris, M.D., Clinical Reviewer
Lucious Lim, M.D., Clinical Reviewer
Sonal Wadhwa, M.D., Clinical Reviewer
Yoriko Harigaya, Clinical Pharmacology Reviewer
William Taylor, Ph.D., Nonclinical Team Leader
Conrad Chen, Ph.D., Nonclinical Reviewer
Linda Ng, Ph.D., Chemistry Reviewer
Shrikant Pagay, Ph.D., Chemistry Reviewer
Yan Wang, Ph.D., Statistical Team Leader
Yunfan Deng, Ph.D., Statistical Reviewer
Judit Milstein, Chief Project Management Staff
Raphael Rodriguez - Regulatory Project Manager

SPONSOR ATTENDEES
Marv Garrett, VP, Regulatory Affairs, Quality Assurance and Compliance
Avery Funk, Manager Regulatory Affairs
George Baklayan, Director, Pharmaceutical Development
Timothy McNamara, VP, Clinical research and Medical Affairs
Kirk McMullin, VP, Operations

Paul Nowacki, Director, Regulatory Affairs
Sharon Klier, Director, Clinical Research
Edward Kim, Manager Clinical Operations

BACKGROUND

ISTA requested this pre-NDA meeting in order to finalize the regulatory submission plans for an NDA on Bromfenac ophthalmic solution, 0.07% for the treatment of inflammation and ocular pain associated with cataract surgery.

DISCUSSION

Preliminary responses to the applicant's Pre-NDA meeting questions were provided via email August 26, 2011. The questions posted by ISTA in the briefing document are described in **bold** format, the preliminary responses sent by the Division are in *italics* format and the discussions held during the meeting on regular font. During this meeting, only questions 2a. and 12 were discussed.

Clinical/Efficacy

Question 1: ISTA is proposing to include these same tables in the ISE for NDA 203168 for Trade Name (bromfenac ophthalmic solution) 0.07% as were provided for Bromday sNDA 021664/S013 and are included in Appendix 1 of the July 29, 2011 submission. Is this acceptable to the Agency?

FDA Response:
In addition to providing the tables listed in Appendix 1, a table which lists subjects who discontinued treatment or the study for any reason should be included as well, along with any adverse events reported by that patient.

Question 2a: We plan to provide a side-by-side comparison of the pooled efficacy data for the (New Trade Name) 0.07% QD vs. the pooled efficacy data (as presented in S-013) for the currently marketed Bromday™ 0.09% QD. Appendix 2 of the submission shows the list of these tables. Is this acceptable to the Agency?

FDA Response:
The side by side comparison of bromfenac ophthalmic solution 0.07% should be with the product's vehicle since the controlled studies compared bromfenac ophthalmic solution 0.07% with its vehicle. Bromday 0.09% was not included as one of the study arms in comparison with bromfenac ophthalmic solution 0.07% and therefore the comparison with Bromday is a cross study comparison. An appropriate comparison between concentrations would be expected to include each concentration in the same study. We recommended that the 0.09% concentration be included as one of the study arms in our response to your SPA dated April 14, 2011.

Meeting Discussion:
The Division recommended head to head comparisons performed in same trial.

Question 2b: ISTA proposes to re-provide the 4 clinical studies that comprise the pooled efficacy data for Bromday™ 0.09% QD that will be used in the side-by-side comparison (Question 2a). These studies were submitted, reviewed and approved in NDA 021664/S-013. ISTA will provide the location in NDA 021664, of other BID bromfenac ophthalmic solution clinical study reports, but we will not provide a hyperlink from NDA 203168 to NDA 021664. Is this acceptable to the Agency?

FDA Response: A hyperlink is not required and as noted in the response to question 2a, a side by side efficacy comparison may be difficult to interpret because it is a cross study comparison.

Question 3: In sNDA 021664/S-013, Bromday™ (bromfenac ophthalmic solution) 0.09%, ISS tables as shown in were submitted, reviewed and approved by the Agency. ISTA is planning to provide integrated analysis of safety data for two well controlled pivotal trials for the new drug product. We are planning to use these same tables for NDA 203168 for Trade Name (bromfenac ophthalmic solution) 0.07%. Is this acceptable to the Agency?

FDA Response: Acceptable

Question 4: We plan to provide side-by-side comparison of the pooled safety data for Trade Name 0.07% QD vs. the pooled side-by-side safety data (as presented in S-013) for Bromday 0.09%. Appendix 4 shows a list of these tables. Is this acceptable to the Agency?

FDA Response: The side by side comparison of bromfenac ophthalmic solution 0.07% should be with the product's vehicle since the controlled studies compared bromfenac ophthalmic solution 0.07% with its vehicle. Bromday 0.09% was not included as one of the study arms in comparison with bromfenac ophthalmic solution 0.07% and therefore the comparison with Bromday is a cross study comparison. We recommended that the 0.09% concentration be included as one of the study arms in our response to your SPA dated April 14, 2011.

Question 5a: For ease of review, ISTA is resubmitting the 4 study reports to NDA 203168 necessary for the side-by-side comparison of the 0.09% QD with the New Trade Name 0.07% QD product. Is this acceptable to the Agency?

FDA Response: Acceptable

Question 5b: As seen in the column, "location of study report" (Appendix 5), we will provide (and not re-submit) the location of previously referenced Clinical Study Reports that were referenced for the approval of Bromday (sNDA 021664/S-013). Is this acceptable to the Agency?

FDA Response: Acceptable.

Question 6: Does the Agency agree that the addition of the baseline observation carried forward (BOCF) analysis and multiple imputations, along with the previously described sensitivity analysis described in the protocol and SAP (Appendix 6), are sufficient to evaluate the robustness of the study results?

FDA Response: The proposed sensitivity analysis seems to be sufficient. The conclusion of the robustness of the study results will be a review issue.

Nonclinical

Question 7: Numerous clinical and non-clinical pharmacokinetic (PK) studies have been performed on various formulations and concentrations (lower and higher than the proposed 0.07% concentration) of bromefenac ophthalmic solutions. These PK studies have been previously submitted to NDA 021664.

The two well controlled, pivotal clinical trials included in this NDA are adequately designed to demonstrate clinical safety and efficacy. ISTA believes that the existing PK data is scientifically adequate to support Trade Name (bromfenac ophthalmic solution) 0.07% and that no additional PK studies are needed. Does the Agency agree?

FDA Response: We agree that the clinical PK studies listed in Appendix 5 in your briefing package are adequate to support filing of an NDA for bromfenac ophthalmic solution 0.07% and no additional clinical PK studies are needed.

Question 8: Numerous animal toxicology studies have been performed on various formulations and concentrations of bromfenac ophthalmic solutions. These toxicology studies have been previously submitted to NDA 021664.

The two well controlled, pivotal clinical trials included in this NDA are adequately designed to demonstrate clinical safety and efficacy. ISTA believes that existing animal toxicology data is scientifically adequate to support the safety of Trade Name (bromfenac ophthalmic solution) 0.07% and no additional toxicology studies are needed. Does the Agency agree?

FDA Response: Please submit to the NDA a comparison of the excipients in the new (0.07% bromfenac) formulation and the previously approved formulation (0.09% bromfenac), and include a discussion of the safety of any new excipients not included in the approved formulation. If you are using new excipients, they may need to be qualified in the future.

Question 9: ISTA plans to submit data files in the CDISC SDTM and ADaM format with the defined xml files for Clinical Study S-00124. Is this acceptable to the Agency

FDA Response: Acceptable

Question 10: This is the first time ISTA will be submitting data files in the CDISC SDTM and Adam format in an NDA. Does CDER have a process for applicants to submit the datasets through the Gateway test environment using the proper M5 folder structure to assure there are no issues prior to filing the NDA?

FDA Response: The process for submitting data files in the CDISC SDTM and ADaM format is the same as when you submit the datasets in other format.

Question 11: Since this is an electronic submission; ISTA understands that the Los Angeles District office will obtain their field copy through their access to the FDA network. ISTA will NOT provide a paper copy of any Module. Is this acceptable to the Agency?

FDA Response: Acceptable

CMC
Question:12a: Does the Agency agree with the stability data plan above for the original NDA submission and the 4 month safety update?

FDA Response: Please follow stability data requirements per ICH Q1 (R2) Stability Guidelines "Stability Testing of New Drug Substances and Products" and submit the required data, i.e., 12 months under long term storage conditions and 6 months under accelerated condition for at least 3 primary batches in commercial container closure system (registration batches) with the original NDA application.

Meeting Discussion:
The Division expects a minimum of 12 months stability data at the time of NDA submission. ISTA raised the possibility of submitting 6 months of stability data in the NDA, with assignment of a shorter shelf-life, or with an extension of dating based on long-term data from 3 production scale batches. The Division responded that they would discuss internally and provide a response at a later date.

Post-Meeting Follow-up response:
Due to the implementation of Good Review Management Practices (GRMP) all NDAs are expected to be complete at the time of initial submission. This includes the primary stability data package, corresponding data summaries and statistical analysis of the data necessary to establish a shelf life. ONDQA recommends the amount of stability data and supporting information provided be sufficient to support a commercially viable product (typically considered to have one year or greater expiry). Therefore, ONDQA, in accordance to ICH Q1A, recommends that a minimum of 12 months real time data and 6 months accelerated data be submitted in the initial NDA submission for at least 3 lots of the proposed commercial drug product. As per GRMP, all NDAs are to be complete in the original submission and any new information, including stability data, submitted subsequent to the original NDA submission may or may not be reviewed as resources allow.

Question:12b: Does the Agency agree that this amount of stability data is acceptable in support of an (b) (4) shelf-life?

FDA Response: Please see our response to Question 12a. Establishing the shelf life is a review issue. The drug product shelf life will be established based on satisfactory review of the data requested above and statistical analysis.

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/s/

RAPHAEL R RODRIGUEZ
12/11/2011

WILEY A CHAMBERS
12/13/2011

4 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this

Drug Product Composition

Component	Function	Bromfenac 0.07% Formulation (%w/v)	Amount /mL (mg/mL)	(b) (4) Batch Composition (b) (4)
Bromfenac sodium sesquihydrate	Active ingredient	0.0805[1]	0.805	
Boric acid				(b) (4)
Sodium borate				
Sodium sulfite				
Edetate disodium (EDTA)				
Tyloxapol				
Benzalkonium chloride	Preservative	0.005	0.05	(b) (4)
Povidone (b) (4				(b) (4)
Sodium hydroxide[2]	pH adjuster	q.s. to pH 7.8	q.s. to pH 7.8	q.s. to pH 7.8
Water for Injection (b) (4) (b) (4)				(b) (4)

[1] Equivalent to 0.07% bromfenac free acid.
[2] Only if necessary to adjust pH to 7.8.

Drug Product Specification

Test	Specification
Product Appearance	Clear, yellow solution
Description: Container	A white plastic bottle with dropper tip and gray cap, with no significant discoloration or physical distortion
Identification (release only)	(b) (4)
Bromfenac Sodium Assay	
Bromfenac Impurities	
Impurity (b) (4)	
Any Individual Specified Impurity (b) (4)	
Any Individual Unspecified Impurity	
pH	
Osmolality	
Benzalkonium Chloride[1]	
EDTA	
Sodium Sulfite	
Sterility	
Particulate Matter (Microscopic Evaluation)	
Particulate Matter (Visual)	
Weight Loss (stability only)	
(b) (4)	

[1] Antimicrobial efficacy test performed if necessary per stability protocol S00243-P.

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/s/

BALAJEE SHANMUGAM
07/25/2012

DOROTA M MATECKA
07/26/2012

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 203-168	**Supplement Number and Type:**	**Established/Proper Name: Bromfenac ophthalmic solution 0.07%**
Applicant: ISTA Pharmaceuticals	**Letter Date: 05-June-2012**	**Stamp Date: 07-June-2012**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		Yes. The meeting minutes have been submitted in the NDA.

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		The facilities have been identified with contact information.
6.	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? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? 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 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)	✓		The Drug substance is referenced to DMF 16414 and a LOA has been provided. Please note that Regis Technologies is the contract manufacturer for the DMF holder.
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. 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)	✓		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. 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)	✓		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	✓		Yes, statement provided in the cover letter and also with the establishment information.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?			The drug substance is referenced to DMF 16414. LOA from the DMF holder is provided in the NDA. Additionally, NDA 020535 has also been referenced and a LOA from Pfizer (Agent for Wyeth) is also provided.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Referenced to DMF
14.	Does the section contain information regarding the characterization of the DS?			Referenced to DMF
15.	Does the section contain controls for the DS?			Referenced to DMF
16.	Has stability data and analysis been provided for the drug substance?	✓		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		✓	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		✓	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?		✓	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		The DMFs referenced for container closure are: a) DMF (b) (4) b) DMF (b) (4) c) DMF (b) (4) d) DMF (b) (4) e) DMF (b) (4) f) DMF (b) (4) g) DMF (b) (4) LOA's have been provided in the NDA.
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			NA
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			NA

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	✓		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	✓		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		Yes. Please see Sections 7 and 24.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
16414	II	Senju Pharmaceuticals	Bromfenac sodium	Feb-17-2012	
(b) (4)	III		(b) (4)	Oct-19-2011	
	III			Oct-19-2011	
	III			Feb-15-2012	
	III			Feb-2-2012	
	III			Apr-18-2012	
	III			Feb-17-2012	
	III			Feb-6-2012	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		The color mock of the carton and container label has not been submitted.

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	✓		1. Please submit color mock of the carton and container labels 2. Provide droplet volume data to demonstrate delivery of uniform and consistent drop volume from the proposed container closure system or indicate where in the NDA this data is provided.

{See appended electronic signature page}

Balajee Shanmugam
CMC Lead
Division of Pre-Marketing Assessment
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Rapti Madurawe Ph.D.
Branch Chief
Branch V
Division of Pre-Marketing Assessment
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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/s/

BALAJEE SHANMUGAM
07/20/2012

DOROTA M MATECKA
07/20/2012