CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208582Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 208582
Review # 2
Nov 28, 2017

Drug Name/Dosage Form	Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution
Strength	0.25%/0.4%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Altaire Pharmaceuticals, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment	13-Jun-2016
Resubmission	28-Jun-2017

Quality Review Team

DISCIPLINE	REVIEWER
Drug Substance	Gaetan Ladouceur
Drug Product	Balajee Shanmugam
Process	Vidya Pai
Microbiology	Denise Miller
Facility	Vidya Pai
Biopharmaceutics	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy
Application Technical Lead	Chunchun Zhang
Environmental Assessment (EA)	Yushi Feng

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	9/7/2017	LoA: 11/9/2015 Reviewed by Gaetan Ladouceur
	Type II			Adequate	11/27/2017	LoA: 6/27/2011 Reviewed by Gaetan Ladouceur for this NDA
	Type III			Adequate	4/14/2015	LoA: 9/18/2015 Reviewed by Kristen Anderson
	Type III			Adequate	5/20/2016	LoA: 8/6/2015 Reviewed by Yushi Feng for NDA 208582
	Type III			Adequate	4/13/2015	LoA: 9/9/2015 Reviewed by Donald Klein

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	(b) (4)	This product during IND development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		11/9/2017	Maria Rivera
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendation

Manufacturing process, biopharmaceutics and quality micro reviewers have recommended approval of the NDA as documented in Review #1 and Addendum #1.

As documented in this review, drug product issues have been satisfactorily resolved; Manufacturing process and quality micro uphold their approval recommendations in this review. The Office of Process and Facilities issued an overall acceptable recommendation for all the facilities on 11-20-2017.

Initially, DMF (b) (4) for Fluorescein Sodium was found inadequate by the DMF reviewer Dr. Qi Liu on 11/7/2017 (b) (4)

(b) (4)

(b) (4) Therefore, the issue identified with the DMF will not adversely impact the quality of the drug product. Furthermore, the DMF was found adequate to support NDA 208582 by Dr. Gaetan Ladouceur on 11/27/2017. Therefore, NDA 208-582 is recommended for Approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: NA
2. Action letter language, related to critical issues such as expiration date. NA
3. Benefit/Risk Considerations: NA

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 [Fluorescein Sodium and Benoxinate Hydrochloride] Quality Summary

The drug product is a combination of two known drug substances, Fluorescein Sodium and Benoxinate Hydrochloride. The applicant cross-referenced the CMC information for the two drug substances to DMF (b) (4) for Fluorescein Sodium and DMF (b) (4) for Benoxinate Hydrochloride respectively.

No extraordinary storage precautions are required for Benoxinate Hydrochloride and a retest period of (b) (4) months at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

No extraordinary storage precautions are required for Fluorescein and a retest period of (b) (4) months for at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

DMF (b) (4) and DMF (b) (4) were found adequate by Gaetan Ladouceur on 9/7/2017 and 11/27/2017, respectively. Therefore, NDA 208582 is recommended for approval from a drug substance perspective.

B. Drug Product [Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution] Quality Summary

Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, 0.25%/0.4% is a sterile, yellow to orange red preserved ophthalmic solution packaged in (b) (4) glass bottle with 5mL fill with (b) (4) (b) (4) cap and (b) (4) liner.
All components in the formulation are of compendial quality. No novel excipients are used in the formulation. The drug product specification includes tests for description, identification, assay, specific gravity, chlorobutanol, impurity, osmolality, pH, particulate matter, minimum fill, deliverable volume and sterility. The proposed specification is acceptable with the exception of the mutagenic impurity (b) (4) which is pending evaluation by the pharm/tox reviewer Maria Rivera. All analytical methods are described in reasonable detail and have been adequately validated.

Batch analyses data is provided for 3 registration batches of drug product in the commercial container closure system with (b) (4) L batch sizes (b) (4) All batches complied with the proposed specification.
Additional assessment in light of the prolonged use of the dropper as a replacement cap is found acceptable by the pharm/tox reviewer Maria Rivera.
Twenty-four months of stability data at long term condition (5°C) and six month data at accelerated condition (25°C/40%RH) are provided for three registration batches. Out of specification assay results were observed for Benoxinate Hydrochloride at the (b) (4) month point (b) (4) No unusual trends are observed (b) (4) (b) (4) (b) (4) at all time points all tested quality attributes remained within the proposed specification. These results support both the expiration dating period and storage statement listed below.

In this review the two non-CR comments on the drug product included in the first review cycle

action letter were reviewed. The extractable/leachables and in-use stability studies are found adequate, refer to the attached drug product review for detailed discussion. Therefore, the NDA is recommended approval from the drug product perspective.

1. Strength: Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, 0.25%/0.4%.
2. Description/Commercial Image: Sterile, yellow to orange red, preserved ophthalmic solution.
3. Summary of Product Design: Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution
4. List of Excipients: See review notes, below.
5. Process Selection (b) (4)
   (b) (4)
   b. Critical equipment: NA
6. Container Closure: (b) (4) glass bottle with (b) (4) cap and (b) (4) liner.
7. Expiration Date & Storage Conditions: 24 months when stored at 2°C–8°C. Can be stored at room temperature for up to 1 month.
8. List of co-packaged components: None.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	(b) (4)
Non Proprietary Name of the Drug Product	Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution
Non Proprietary Name of the Drug Substance	Fluorescein Sodium and Benoxinate Hydrochloride
Proposed Indication(s) including Intended Patient Population	For procedures requiring a disclosing agent in combination with a topical ophthalmic anesthetic agent (b) (4) (b) (4)
Duration of Treatment	NA
Maximum Daily Dose	Usual dosage: 1-2 drops per eye (b) (4) (b) (4)
Alternative Methods of Administration	None

D. Biopharmaceutics Assessment

Biowaiver

Fluorescein is a diagnostic dye and not absorbed, and benoxinate is a rapidly acting topical anesthetic. Evidence of BA/BE is not provided and will not be needed for this ophthalmic locally acting product applied topically as drops onto the eye for diagnostic/anesthetic purposes only, because the drugs are not expected to reach the systemic circulation and because of the long history of clinical safety and effectiveness of fluorescein and benoxinate. Therefore, even if not requested, the biowaiver is granted.

Bridging the formulations described in the literature and the proposed drug product
The Application is relying on the published literature for safety and efficacy of the proposed drug product. Therefore, there is a need to establish a bridge between the products described in the literature and the proposed drug product.

The literature references 1-5 and 10-13 from Section 5.4 of the submission are identified as the key literature references that support the approval of the proposed drug product.
Fluress (sodium fluorescein and benoxinate HCl) manufactured by Akorn was listed as the drug product used in the following references 1, 2, 3, 5, 10, 11, 12, and 13. Accufloro (sodium fluorescein and benoxinate) manufactured by Altaire Pharmaceuticals was listed as the drug product used in reference 4.

(b) (4)

(b) (4)

In conclusion, from the Biopharmaceutics perspective there is an adequate bridge between the formulations described in the literature and the proposed drug product.

E. Novel Approaches: None

F. Any Special Product Quality Labeling Recommendations: None

G. Life Cycle Knowledge Information

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach (b) (4)	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site[3]	H		L	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	H		L	No endotoxin testing required.
Assay (API), stability	Formulation Container closure[1] Raw materials	L		L	
Assay (preservative)	Formulation Container closure[1] Process parameters Scale/equipment	L		L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	M		L	
pH	Formulation Container closure[1] Process parameters Scale/equipment	L		L	
Particulate matter	Formulation Container closure[1] Process parameters Scale/equipment	M		M	

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.

QUALITY ASSESSMENT

MICROBIOLOGY

Product Background: This is a currently marketed unapproved drug product that is a topical ophthalmic anesthetic.

ANDA: **208-582**

Drug Product Name / Strength: (b) (4) (Fluorescein Sodium and Benoxinate Hydrocholride Ophthalmic Solution USP)

Route of Administration: Topical ophthalmic

Applicant Name: Altaire Pharmaceutical

Manufacturing Site:

Altaire Pharmaceutical
311 West Lane
Aquebogue NY 11931

(b) (4)

Review Recommendation: Adequate

Review Summary: The last review cycle did not have any outstanding issues from quality microbiology; however the CR letter cited an unfinished microbiology issue of data pending from the response to an information request. (b) (4) (b) (4) The data was provided in this cycle and was acceptable.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
28 June 2017	28 June 2017	N/A	NA

Highlight Key Outstanding Issues from Last Cycle: See review summary.

Remarks: NA

Concise Description Outstanding Issues Remaining: NA

Supporting Documents:
DMA review N208582MR01.doc

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance

P Drug Product

There were no manufacturing changes provided from the first cycle review (see DMA review N208582MR01.doc).

(b) (4)

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Denise A. Miller 26 September 2017

Secondary Reviewer Name and Date: Bryan Riley

Bryan Riley

Digitally signed by Bryan Riley
Date: 10/12/2017 08:18:20AM
GUID: 503450f200004f5816a1d3ae902b5e91

Denise Miller

Digitally signed by Denise Miller
Date: 10/12/2017 08:08:32AM
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NDA 208582

Product Quality Assessment (Addendum #2 to Addendum #1)

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

Date: June-15-2016

Re: Revised non-CR comments be included in the CR letter

In response to the Information Request dated March 16, 2016, the applicant submitted Amendments dated June 6 and June 9, 2016 which provided information on in-use stability to support the label storage statement and volatile impurities for the extractable/leachables, respectively. The new information will not be reviewed as it was submitted late in the review cycle. Also, one non-CR comment from the quality micro review mentioned in Addendum #1 should be included in the CR letter.

The following non-CR comments should be included in the CR letter:

1) We acknowledge your amendments of June 6, 2016 and June 9, 2016 in response to our Information Request dated March 16, 2016 on the in-use stability to support the label storage statement and volatile impurities for the extractable/leachable study. We are unable to review the new information as it was submitted late in the review cycle.

(b) (4)

[redacted]

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

Chunchun Zhang, Ph.D.
ATL for 208582

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: 2016.06.15 11:40:16 -04'00'

Recommendation: Complete Response

NDA 208582
Addendum #1 to Review # 1
June 7, 2016

Drug Name/Dosage Form	Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution
Strength	0.25%/0.4%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Altaire Pharmaceuticals, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	22-Dec-2015
Amendment	22-Feb-2016
Amendment	29-Feb-2016
Amendment	22-Mar-2016
Amendment	04-Apr-2016
Amendment	11-Apr-2016
Amendment	29-Apr-2016
Amendment	16-May-2016
Amendment	23-May-2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gaetan Ladouceur, Ph.D.	ONDP/DNDAPI/NDBI
Drug Product	Yushi Feng, Ph.D.	ONDP/DNDP-I/Branch III
Process	Vidya Pai, Ph.D.	OPF/DBAIII/PABVII
Microbiology	Denise Miller	OPF/DMA/MABII
Facility	Vidya Pai, Ph.D.	OPF/DBAIII/PABVII
Biopharmaceutics	Banu Zolnik, 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)	Yushi Feng, Ph.D.	ONDP/DNDP-I/Branch III

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	5/25/2016	LoA: 11/9/2015 Reviewed by Gaetan Ladouceur
	Type II			Inadequate	4/7/2016	LoA: 6/27/2011 Reviewed by Qi Liu
	Type III			Adequate	4/14/2015	LoA: 9/18/2015 Reviewed by Kristen Anderson
	Type III			Adequate	5/20/2016	LoA: 8/6/2015 Reviewed by Yushi Feng for NDA 208582
	Type III			Adequate	4/13/2015	LoA: 9/9/2015 Reviewed by Donald Klein

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	(b) (4)	This product during IND development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		6/2/2016	Maria Rivera
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations

Manufacturing process and biopharmaceutics reviewers have recommended approval of the NDA as documented in Review #1.

As documented in this Addendum, microbiological issues have been satisfactorily resolved. DMF (b) (4) for the drug substance Fluorescein Sodium found inadequate on 4/7/2016 remains inadequate at this time.There are two pending IRs for the drug product and therefore the drug product is deficient.

The outcome of the most recent inspection of the drug substance manufacturing facility, (b) (4) has resulted in Office of Process and Facilities recommending Withhold.

Because of the deficiency of DMF (b) (4) for Fluorescein Sodium and Withhold recommendation for (b) (4) facility, NDA 208-582 is recommended for Complete Response from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: As described above.
2. Action letter language, related to critical issues such as expiration date: The following CR statements about the unacceptable manufacturing facility (b) (4) and inadequate DMF (b) (4) should be included in the CR letter:

   1) *During a recent inspection of the (b) (4) drug substance manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

   2) *Your application referenced the Drug Master File (DMF) (b) (4) This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on April 7,2016. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.*

   The following non-CR comments should be included in the CR letter:

   1) *In an Information Request dated March 16, 2016, the FDA requested additional information/data on volatile impurities for the*

extractable/leachable study. In a follow-up to the Information Request on April 29, 2016, you responded that the results will be available by May 16, 2016. However, no additional information/data has been submitted to date.

2) *We acknowledge your amendment of June 6, 2016 in response to our Information Request dated March 16, 2016 on the in-use stability to support the label storage statement. We are unable to review the new information as it was submitted late in the review cycle.*

3. Benefit/Risk Considerations: Not applicable for CR

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 [Fluorescein Sodium and Benoxinate Hydrochloride] Quality Summary

The drug product is a combination of two known drug substances, Fluorescein Sodium and Benoxinate Hydrochloride. The applicant cross-referenced the CMC information for the two drug substances to DMF (b) (4) for Fluorescein Sodium and DMF (b) (4) for Benoxinate Hydrochloride respectively.

No extraordinary storage precautions are required for Benoxinate Hydrochloride and a retest period of (b) (4) months at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

No extraordinary storage precautions are required for Fluorescein and a retest period of (b) (4) months for at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

DMF (b) (4) was found adequate by Gaetan Ladouceur on 5/25/2016, while DMF (b) (4) was found inadequate by Qi Liu on 4/7/2016. Therefore NDA 208582 is found deficient from a drug substance perspective.

B. Drug Product [Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution] Quality Summary

Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, 0.25%/0.4% is a sterile, yellow to orange red preserved ophthalmic solution packaged in (b) (4) glass bottle with 5mL fill with (b) (4) cap and (b) (4) liner.

All components in the formulation are of compendial quality. No novel excipients are used in the formulation.

The drug product specification includes tests for description, identification, assay, specific gravity, chlorobutanol, impurity, osmolality, pH, particulate matter,

minimum fill, deliverable volume and sterility. The proposed specification is acceptable with the exception of the mutagenic impurity (b) (4) (b) (4) which is pending evaluation by the pharm/tox reviewer Maria Rivera. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, Additionally, all microbiology related issues concerning the drug product have been satisfactorily resolved.

Batch analyses data is provided for 3 registration batches of drug product in the commercial container closure system with (b) (4) L batch sizes (b) (4) (b) (4) All batches complied with the proposed specification.

Additional assessment in light of the prolonged use of the dropper as a replacement cap is found acceptable by the pharm/tox reviewer Maria Rivera.

Assessment of the leachable/extractable study on volatile impurities is pending since the company has not responded to the IR since June 7, 2016.

Twenty-four months of stability data at long term condition (5°C) and six month data at accelerated condition (25°C/40%RH) are provided for three registration batches. Out of specification assay results were observed for Benoxinate Hydrochloride at the (b) (4)-month point (b) (4) No unusual trends are observed (b) (4) (b) (4) at all time points all tested quality attributes remained within the proposed specification. These results supports both the expiration dating period and storage statement listed below. The company submitted in-use stability data on June 6, 2016 to support the label storage statement of 25°C for up to 1 month. Since the response was submitted very late in the review cycle, the new information will not be reviewed. This will be conveyed in the Action Letter as a non-CR comment. Because of the issues detailed above, the NDA is deficient from the drug product perspective.

1. Strength: Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, 0.25%/0.4%.
2. Description/Commercial Image: Sterile, yellow to orange red, preserved ophthalmic solution.
3. Summary of Product Design: Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution
4. List of Excipients: See review notes, below.
5. Process Selection (b) (4) (b) (4)
6. Container Closure: (b) (4) glass bottle with (b) (4) cap and (b) (4) liner.

7. Expiration Date & Storage Conditions: 24 months when stored at 2ºC – 8ºC.
8. List of co-packaged components: None.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	(b) (4)
Non Proprietary Name of the Drug Product	Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution
Non Proprietary Name of the Drug Substance	Fluorescein Sodium and Benoxinate Hydrochloride
Proposed Indication(s) including Intended Patient Population	For procedures requiring a disclosing agent in combination with a topical ophthalmic anesthetic agent (b) (4) (b) (4)
Duration of Treatment	NA
Maximum Daily Dose	Usual dosage: 1-2 drops per eye (b) (4) (b) (4)
Alternative Methods of Administration	None

D. Biopharmaceutics Assessment

Biowaiver

Fluorescein is a diagnostic dye and not absorbed, and benoxinate is a rapidly acting topical anesthetic. Evidence of BA/BE is not provided and will not be needed for this ophthalmic locally acting product applied topically as drops onto the eye for diagnostic/anesthetic purposes only, because the drugs are not expected to reach the systemic circulation and because of the long history of clinical safety and effectiveness of fluorescein and benoxinate. Therefore, even if not requested, the biowaiver is granted.

Bridging the formulations described in the literature and the proposed drug product

The Application is relying on the published literature for safey and efficacy of the proposed drug product. Therefore, there is a need to establish a bridge between the products described in the literature and the proposed drug product.

The literature references 1-5 and 10-13 from Section 5.4 of the submission are identified as the key literature references that support the approval of the proposed drug product. Fluress (sodium fluorescein and benoxinate HCl) manufactured by Akorn was listed as the drug product used in the following references 1, 2, 3, 5, 10, 11, 12, and 13. Accufloro (sodium fluorescein and benoxinate) manufactured by Altaire Pharmaceuticals was listed as the drug product used in reference 4.

(b) (4)

(b) (4)

(b) (4)

In conclusion, from the Biopharmaceutics perspective there is an adequate bridge between the formulations described in the literature and the proposed drug product.

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 (b) (4)	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	• Formulation • Container closure[1] • Process parameters • Scale/equipment • Site	H		H	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M		L	No endotoxin testing required.
Assay (API), stability	• Formulation • Container closure[1] • Raw materials	L		L	
Assay (preservative)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	L		L	

			(b) (4)		
Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	**M**		**L**	
Osmolality	• Formulation • Container closure[1] • Process parameters • Scale/equipment	**L**		L	
pH	• Formulation • Container closure[1] • Process parameters • Scale/equipment	**L**		**L**	
Particulate matter	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M		M	

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.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

NDA 208-582 is recommended for Complete Response based on the issues identified by OPF (facilities) and ONDP (inadequate DMF for the drug substance Fluorescein Sodium).

Chunchun Zhang -S

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

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OPQ/OPF/DIA/Branch III

Secondary Review Comments and Concurrence:

Derek S. Smith, Ph.D., 5/19/2016

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Recommended for approval, see Review #1.

ASSESSMENT OF MICROBIOLOGY

3. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Product Quality Microbiology Assessment

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

S DRUG SUBSTANCE – NA; Drug substance is not sterile.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – Yellow to orange red liquid. (b) (4)
- Drug product composition – The composition of the drug product is copied below into Table 1 (copied from section 2.3.P.1.2 of the submission):

Table 1: Composition of Drug Product

mg/mL	Ingredients	CAS #	Percentage	Role in Formulation
(b) (4)	Fluorescein USP	(b) (4)	0.22 (b) (4) % *	Active
	Sodium Hydroxide NF		(b) (4)	pH Adjuster
	Benoxinatae Hydrochloride USP		0.4%	Active
	Chlorobutanol NF		1.1%	Preservative
	Povidone (b) (4) USP		(b) (4)	(b) (4)
	Hydrochloric Acid (b) (4) % NF			pH Adjuster
	Boric Acid NF			(b) (4)
	Water for Injection USP		-	
Qs	May contain Hydrochloric Acid and/or Sodium Hydroxide to adjust a target pH of (b) (4)		-	

(b) (4)

- Description of container closure system –
  - (b) (4) glass bottle
  - (b) (4) cap and (b) (4) liner
  - Dropper/cap (to be co-packaged with the bottle)

(b) (4)

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3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

There were no deficiencies from a quality microbiology perspective noted in the information provided. There is one non –deficiency comment to be provided to the sponsor.

(b) (4)

[redacted]

Reviewer's Assessment: The information provided is acceptable.

2.3.P.7 Container/Closure System

4. 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?

Applicant's Response:

Reviewer's Assessment: see review of container closure in Question 29.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

5. 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:

Reviewer's Assessment: **See Question 29.**

6. 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:

Reviewer's Assessment: See Question 29.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:The recommendation is to approve from a quality microbiology perspective.
Denise A. Miller
Division of Microbiolgoy Assessment

Secondary Review Comments and Concurrence:
I concur with the microbiology review assessment and approval recommendation.
Neal J. Sweeney, Ph.D. 26May2016
Microbiology Quality Assessment Lead (Acting)

OPQ/OPF/DMA/Branch II

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Recommended for approval, see Review #1.

Recommendation: Pending Recommendation

NDA 208582
Review # 1
May 24, 2016

Drug Name/Dosage Form	Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution USP
Strength	0.25%/0.4%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Altaire Pharmaceuticals, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	22-Dec-2015
Amendment	22-Feb-2016
Amendment	29-Feb-2016
Amendment	22-Mar-2016
Amendment	04-Apr-2016
Amendment	11-Apr-2016
Amendment	29-Apr-2016
Amendment	16-May-2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gaetan Ladouceur, Ph.D.	ONDP/DNDAPI/NDBI
Drug Product	Yushi Feng, Ph.D.	ONDP/DNDP-I/Branch III
Process	Vidya Pai, Ph.D.	OPF/DBAIII/PABVII
Microbiology	Denise Miller, Ph.D.	OPF/DMA/MABII
Facility	Vidya Pai, Ph.D.	OPF/DBAIII/PABVII
Biopharmaceutics	Banu Zolnik, 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)	Yushi Feng, Ph.D.	ONDP/DNDP-I/Branch III

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Pending		LoA: 11/9/2015
	Type II			Pending		LoA: 6/27/2011
	Type III			Adequate	4/14/2015	LoA: 9/18/2015 Reviewed by Kristen Anderson.
	Type III			Adequate	5/20/2016	LoA: 8/6/2015 Reviewed by Yushi Feng for NDA 208582.
	Type III			Adequate	4/13/2015	LoA: 9/9/2015 Reviewed by Donald Klein.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	(b) (4)	This product during IND development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Pending		5/19/2016	Maria Rivera
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations

Satisfactory information and responses have been submitted to support the manufacturing process and biopharmaceutics aspects.

At the current time, GMP inspection of the manufacturing facilities supporting the NDA application indicates lack of compliance and OPF has issued an overall recommendation of "Withhold". In particular, the compliance status of the drug substance manufacturing facility, [redacted] (b) (4) was found unacceptable.

There are several unresolved product quality issues and therefore a final assessment of drug substance, drug product and quality micro is pending at this time. Once the responses are evaluated and assessments become available, a final recommendation from OPQ will be documented in an addendum.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: NA
2. Action letter language, related to critical issues such as expiration date: This will be addressed in the addendum.
3. Benefit/Risk Considerations: NA

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

II. Summary of Quality Assessments

A. Drug Substance [Fluorescein Sodium and Benoxinate Hydrochloride] Quality Summary

The drug product is a combination of two known drug substances, Fluorescein Sodium and Benoxinate Hydrochloride. The applicant cross-referenced the CMC information for the two drug substances to DMF [redacted] (b) (4) for Fluorescein Sodium and DMF [redacted] (b) (4) for Benoxinate Hydrochloride respectively.

No extraordinary storage precautions are required for Benoxinate Hydrochloride and a retest period of [redacted] (b) (4) months [redacted] (b) (4) is supported by drug substance stability data.

No extraordinary storage precautions are required for Fluorescein and a retest period of [redacted] (b) (4) months [redacted] (b) (4) is supported by drug substance stability data.

Both DMFs have outstanding IRs to be resolved and therefore is "Deficient" at this time.

B. Drug Product [Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution] Quality Summary

Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, 0.25%/0.4% is a sterile, yellow to orange red (b) (4), preserved ophthalmic solution packaged in (b) (4) glass bottle with 5mL fill with (b) (4) (b) (4) cap and (b) (4) liner.

All components in the formulation are of compendial quality. No novel excipients are used in the formulation.

The drug product specification includes tests for description, identification, assay, specific gravity, chlorobutanol, impurity, osmolality, pH, particulate matter, minimum fill, deliverable volume and sterility. The proposed specification is acceptable with the exception of the mutagenic impurity (b) (4) (b) (4) which is pending evaluation by the pharm/tox reviewer Maria Rivera. All analytical methods are described in reasonable detail and have been adequately validated. Additionally, all microbiology related issues concerning the drug product are pending.

Batch analyses data is provided for 3 registration batches of drug product in the commercial container closure system with (b) (4) L batch sizes (b) (4) . All batches complied with the proposed specification.

Assessment of the leachable/extractable study on volatile impurities is pending since the company is yet to respond to the IR. Additional assessment in light of the prolonged use of the dropper as a replacement cap is pending by the pharm/tox reviewer Maria Rivera.

Twenty-four months of stability data at long term condition (5°C) and six month data at accelerated condition (25°C/40RH) are provided for three registration batches. Out of specification assay results were observed for Benoxinate Hydrochloride at the 6-month point under accelerated condition. No unusual trends are observed (b) (4) (b) (4) (b) (4) all time points all tested quality attributes remained within the proposed specification. These results supports both the expiration dating period and storage statement listed below. However, in-use stability data to support the label storage statement of 25°C for up to 1 month is pending. Therefore, the NDA is deficient from the drug product perspective.

1. Strength: Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, 0.25%/0.4%.
2. Description/Commercial Image: Sterile, yellow to orange red, preserved ophthalmic solution.
3. Summary of Product Design: Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution
4. List of Excipients: See review notes, below.
5. Process Selection (b) (4)

(b) (4)

b. Critical equipment: NA

6. Container Closure: (b) (4) glass bottle with (b) (4) cap and (b) (4) liner.
7. Expiration Date & Storage Conditions: 24 months when stored at 2ºC – 8ºC.
8. List of co-packaged components: None.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	(b) (4)
Non Proprietary Name of the Drug Product	Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution
Non Proprietary Name of the Drug Substance	Fluorescein Sodium and Benoxinate Hydrochloride
Proposed Indication(s) including Intended Patient Population	For procedures requiring a disclosing agent in combination with a topical ophthalmic anesthetic agent (b) (4) (b) (4)
Duration of Treatment	NA
Maximum Daily Dose	Usual dosage: 1-2 drops per eye (b) (4) (b) (4)
Alternative Methods of Administration	None

D. Biopharmaceutics Assessment

Biowaiver

Fluorescein is a diagnostic dye and not absorbed, and benoxinate is a rapidly acting topical anesthetic. Evidence of BA/BE is not provided and will not be needed for this ophthalmic locally acting product applied topically as drops onto the eye for diagnostic/anesthetic purposes only, because the drugs are not expected to reach the systemic circulation and because of the long history of clinical safety and effectiveness of fluorescein and benoxinate. Therefore, even if not requested, the biowaiver is granted.

Bridging the formulations described in the literature and the proposed drug product

The Application is relying on the published literature for safey and efficacy of the proposed drug product. Therefore, there is a need to establish a bridge between the products described in the literature and the proposed drug product.

The literature references 1-5 and 10-13 from Section 5.4 of the submission are identified as the key literature references that support the approval of the proposed drug product. Fluress (sodium fluorescein and benoxinate HCl) manufactured by Akorn was listed as the drug product used in the following references 1, 2, 3, 5, 10, 11, 12, and 13. Accufloro (sodium fluorescein and benoxinate) manufactured by Altaire Pharmaceuticals was listed as the drug product used in reference 4.

(b) (4)

(b) (4)

In conclusion, from the Biopharmaceutics perspective there is an adequate bridge between the formulations described in the literature and the proposed drug product.

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 (b) (4)	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	• Formulation • Container closure[1] • Process parameters • Scale/equipment • Site	H		H	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M		L	No endotoxin testing required.

			(b) (4)		
Assay (API), stability	• Formulation • Container closure[1] • Raw materials	**L**		**L**	
Assay (preservative)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	**L**		**L**	
Uniformity of Dose (Fill Vol/ Deliverable volume)	• Formulation • Container closure[1] • Process parameters • Scale/equipment	**M**		**L**	
Osmolality	• Formulation • Container closure[1] • Process parameters • Scale/equipment	**L**		L **L**	
pH	• Formulation • Container closure[1] • Process parameters • Scale/equipment	**L**		**L**	
Particulate matter	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M		M	

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.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

A final assessment on the status of the facilities from OPF and recommendations from drug substance, drug product and quality micro are pending at this time. When the assessments are available, an overall recommendation from OPQ will be documented in an Addendum.

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

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: 2016.05.24 18:29:41 -04'00'

95 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

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

Not Applicable. The proposed drug product is an ophthalmic solution, therefore, a dissolution test is not applicable.

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

Not Applicable. The Applicant did not conduct any clinical study during development, and the NDA is relying on the published literature.

39.1 Bridging the formulations described in the literature and the proposed drug product.

The Application is relying on the published literature for safey and efficacy of the proposed drug product. There were a total of 29 publications submitted. The Medical Reviewer identified nine literature references (Refs 1-5 and 10-13 from Section 5.4) as the key literature references that support the approval of the proposed drug product. Fluress (sodium fluorescein and benoxinate HCl) manufactured by Akorn was listed as the drug product used in the following references 1, 2, 3, 5, 10, 11, 12, and 13. Accufloro (sodium fluorescein and benoxinate) manufactured by Altaire Pharmaceuticals was listed as the drug product used in reference 4. The Table below shows the comparative composition information of the formulation used in the studies in the literature and the proposed drug product (prepared by the Reviewer).

(b) (4)

[redacted]

Reviewer's Assessment:

(b) (4)

[redacted]

In conclusion, from the Biopharmaceutics perspective there is an adequate bridge between the formulations described in the literature and the proposed drug product.

39.2 Biowaiver

This NDA is a 505(b)(2) application which relies solely on published literature to support the drug product's safety and efficacy. The systemic exposure to fluorescein and benoxinate following topical ocular administration of fluorescein sodium and benoxinate HCl (0.25%/0.4%) ophthalmic solution has not been studied.The Applicant did not request the waiver of the requirement to provide evidence of in vivo bioavailability (BA) or bioequivalence (BE).

Reviewer's Assessment:

Fluorescein is a diagnostic dye and not absorbed, and benoxinate is a rapidly acting topical anesthetic.The proposed drug product will be administered by giving one to two drops in each eye before operation. Evidence of BA/BE will not be needed for this ophthalmic locally acting product applied topically as drops onto the eye for diagnostic/anesthetic purposes only, because the drugs are not expected to reach the systemic circulation and because of the long history of clinical safety and effectiveness of fluorescein and benoxinate. Therefore, even if not requested, the biowaiver is granted.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From the Biopharmaceutics perspective, NDA 208582 for Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution USP, 0.25%/0.4% is recommended for **APPROVAL.**

5/18/16

Banu Sizanli Zolnik, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
ONDP, OPQ

Secondary Review Concurrence and Signature:

I concur with Dr. Sizanli Zolnik's assessment and recommendation.

5/19/2016

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
ONDP, OPQ

ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Reviewer's Assessment:

2.3.P.7 Container/Closure System

41. 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?

Applicant's Response:

Reviewer's Assessment:

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. 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:

Reviewer's Assessment:

43. 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:

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Secondary Review Comments and Concurrence:

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

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

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

The applicant claims categorical exclusion under 21 CFR 25.31(a) from filing Environmental Impact Assessment Statement with respect to this application.

The applicant claims that the proposed action does not alter significantly the concentration or distribution of the drug substances, their metabolites, or degradation products in the environment. The applicant further claims that the drug product, Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution USP (0.25%/0.4%), covered by this application is not expected to increase the use of the active moieties. The drug product to be manufactured by Altaire Pharmaceuticals, Inc., USA will be administered at the same dosage levels, the same duration and for the same indications as the unapproved drug products currently on the market.
The applicant certifies that the firm is in full compliance with applicable local, state and federal environmental rules and regulations.

Reviewer's Assessment: ADEQUATE

Categorical exclusion per 21 CFR 25.31(a) is claimed and can be granted.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: ADEQUATE
The claim is reasonable and is acceptable.
Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
May 10, 2016.

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D., Branch Chief (Acting), Branch 3, ONDP I.
May 22, 2016.

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

Labeling & Package Insert

1. Package Insert

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

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4)

(b) (4) (fluorescein sodium and benoxinate hydrochloride Ophthalmic Solution (b) (4) 0.25%/0.4%) (b) (4)

DOSAGE FORMS AND STRENGTHS

(b) (4) ophthalmic solution: 0.25% /0.4% [3].

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name is not presented.	DEFICIENT
Dosage form, route of administration Controlled drug substance symbol (if applicable)		ADEQUATE N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		ADEQUATE

Conclusion: DEFICIENT
Recommended changes are highlighted.

(b) "Full Prescribing Information" Section

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

Fluorescein sodium and benoxinate hydrochloride Ophthalmic Solution (b) (4)
0.25%/0.4%: (b) (4) yellow to orange-red (b) (4) solution (b) (4)
containing fluorescein sodium 0.25% and benoxinate hydrochloride 0.4%.

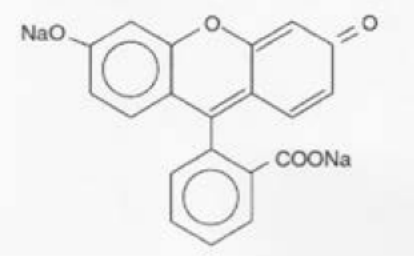
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		ADEQUATE
Strengths: in metric system		ADEQUATE
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Update description to "yellow to orange red solution (b) (4)	DEFICIENT

Conclusion: DEFICIENT
Recommended changes are highlighted.

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

(b) (4) (fluorescein sodium and benoxinate hydrochloride Ophthalmic Solution (b) (4) 0.25%/0.4%(b) is a sterile disclosing agent (b) (4) for ophthalmic use (b) (4)

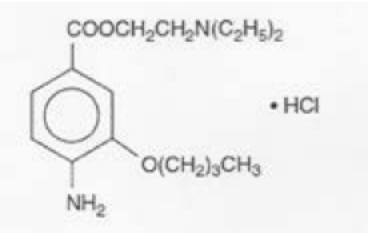
Fluorescein sodium is represented by the following structural formula.



$C_{20}H_{10}Na_2O_5$ Mol. Wt. 376.27

Chemical Name: Spiro [isobenzofuran-1 (3*H*),9'-9[9*H*] xanthene]-3-one, 3',6' dihydroxy, disodium salt.

Benoxinate hydrochloride is represented by the following structural formula:



$C_{17}H_{28}N_2O_3 \bullet HCl$ Mol. Wt. 344.88

Chemical Name: 2-(Diethylamino) etyl 4-amino-3(b)butoxybenzoate monohydrochloride.

EACH mL CONTAINS: ACTIVES: Fluorescein Sodium 2.5 mg (0.25%) equivalent to Fluorescein 2.2 mg (0.22%), Benoxinate Hydrochloride 4 mg (0.4%); INACTIVES: Povidone, Boric Acid, Water for Injection. Hydrochloric Acid may be added to adjust pH (4.3 – 5.3). PRESERVATIVE: Chlorobutanol 1.1%.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name is not presented.	DEFICIENT
Dosage form and route of administration		DEFICIENT
Active moiety expression of strength with equivalence statement for salt (if applicable)		DEFICIENT
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		ADEQUATE
Statement of being sterile (if applicable)		DEFICIENT
Pharmacological/ therapeutic class		ADEQUATE
Chemical name, structural formula, molecular weight		ADEQUATE
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		ADEQUATE

Conclusion: DEFICIENT
Recommended changes are highlighted.

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

Fluorescein sodium and benoxinate hydrochloride Ophthalmic Solution (b) (4) 0.25%/0.4% is a yellow to orange red solution (b) (4) supplied in a glass bottle~~d~~ with a sterilized dropper in the following size: 5mL (b) (4) packaged 5 mL bottles

Storage: Store in refrigerator at 2°-8°C (36°-46°F). Can be stored at room temperature for up to 1 month. Keep tightly closed.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		ADEQUATE
Available units (e.g., bottles of 100 tablets)		DEFICIENT
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		DEFICIENT
Special handling (e.g., protect from light, do not freeze)		ADEQUATE
Storage conditions	Storage conditions are provided. However, the required in-use stability data to support the statement "Can be stored at room temperature for up to 1 month." have not been provided. The applicant indiated that the required study is ongoing and results will be submitted around 6/01/2016.	DEFICIENT

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

Manufactured by:
ALTAIRE Pharmaceuticals, Inc.
Insert Street Address
Aquebogue, NY 11931

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

Conclusion: DEFICIENT
Recommended changes are highlighted.

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))		ADEQUATE
Net contents* (21 CFR 201.51(a))		ADEQUATE
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		ADEQUATE
Lot number per 21 CFR 201.18		DEFICIENT
Expiration date per 21 CFR 201.17		DEFICIENT
"Rx only" statement per 21 CFR 201.100(b)(1)		ADEQUATE
Storage (not required)	Storage conditions are included in the immediate container label. However, the required in-use stability data to support the statement "Can be stored at room temperature for up to 1 month." have not been provided. The applicant indiated that the required study is ongoing and results will be submitted around 6/01/2016.	DEFICIENT
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)***		DEFICIENT
Name of manufacturer/distributor (21 CFR 201.1)		ADEQUATE
Others		

*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: DEFICIENT
Lot number and expiration date are not presented on the immediate container label.
Storage conditions are included in the immediate container label. However, the required in-use stability data to support the statement “Can be stored at room temperature for up to 1 month.” have not been provided. The applicant indiated that the required study is ongoing and results will be submitted around 6/01/2016.
Bar code is not presented on the immediate container label.
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. Change from (b) (4) (b) (4) “ACTIVES: Fluorescein Sodium 2.5 mg (0.25%) equivalent to Fluorescein 2.2 mg (0.22%)”.

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))	The established name is printed in letters that are less than half the size of the letters comprising the proprietary name.	DEFICIENT
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		DEFICIENT
Expiration date per 21 CFR 201.17		DEFICIENT
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	Storage conditions are included in the carton label. However, the required in-use stability data to support the statement "Can be stored at room temperature for up to 1 month." have not been provided. The applicant indiated that the required study is ongoing and results will be submitted around 6/01/2016.	DEFICIENT
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)		DEFICIENT

"Keep out of reach of children" (optional for Rx, required for OTC)		ADEQUATE
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		ADEQUATE

Conclusion: DEFICIENT
The established name is printed in letters that are less than half the size of the letters comprising the proprietary name.
Lot number and expiration date are not presented on the carton label.
Storage conditions are included in the carton label. However, the required in-use stability data to support the statement "Can be stored at room temperature for up to 1 month." have not been provided. The applicant indiated that the required study is ongoing and results will be submitted around 6/01/2016.
Change from "See package insert" to "See package insert for dosage information".
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. Change from (b) (4) (b) (4) ACTIVES: Fluorescein Sodium 2.5 mg (0.25%) equivalent to Fluorescein 2.2 mg (0.22%)".

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: DEFICIENT
Changes are recommended for the container labels. Review is based on the latest labeling information submitted in Supporting Document Number: 1, eCTD Sequence Number 0000, Submit Date: 12/22/2015.
Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
May 20, 2016.

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D., Branch Chief (Acting), Branch 3, ONDP I.
May 22, 2016.