CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211039Orig1s000

PRODUCT QUALITY REVIEW(S)

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Approval

Satisfactory information and responses have been submitted to support product quality (biopharmaceutics, drug substance, and drug product), refer to IQA#1 dated 6/11/2019. All responses to deficiencies are found acceptable from manufacturing process and quality microbiology perspective.

The outcome of the most recent inspection of the drug substance Fluorescein Sodium manufacturing facility (b) (4) *for this resubmission has resulted in Office of Pharmaceutical Manufacturing Assessment (OPMA) recommending Approval. An overall acceptable cGMP recommendation for all the facilities was issued on 2/27/2020.*

Therefore, NDA 211039 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 discussion.

The following PMCs have been concurred by the applicant on Mar 4, 2020 and should be included in the Action Letter:

1. Post Marketing Commitment # (b) (4) *1: Provide the compatibility study reports of the bulk solution statically contacting with each* (b) (4) *component* (b) (4) *for 24 hours. Establish a control strategy (* (b) (4) *to mitigate the risks from the incompatibility of the* (b) (4) *components* (b) (4)

Final protocol submission date: May 15, 2020; study completion: August 15, 2020; and final report submission: October 15, 2020.

2. Post Marketing Commitment # (b) (4) *-2:* (b) (4) *Establish a procedure which ensures that bulk solution* (b) (4)

(b) (4) update the master batch record accordingly.
Final protocol submission date: May 15, 2020; study completion: August 15, 2020; and final report submission: October 15, 2020.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, (b) (4) %/0.4% is a sterile and preserved ophthalmic solution and packaged into 6cc Type (b) (4) amber glass vials (5mL fill volume) with a polypropylene cap/ (b) (4) and then the filled vial is labeled and placed into a unit carton. A sterile dropper is included for administration of the drug product to the eye.

Proposed Indication(s) including Intended Patient Population	For procedures requiring a disclosing agent in combination with topical ophthalmic anesthetic
Duration of Treatment	One or two drops topically in the eye
Maximum Daily Dose	As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The applicant cross-referenced the CMC information for the drug substance Fluorescein Sodium to DMF (b) (4) and drug substance Benoxinate Hydrochloride to DMF (b) (4). DMFs (b) (4) and (b) (4) were found adequate by Dr. Hari Sarker.

Drug Product: Adequate

No new drug product information is submitted in the resubmission. Refer to the drug product review # 1. The expiration date of 21 months is granted when stored at 2 °C- 8 °C.

Labeling: Adequate

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

Manufacturing: Adequate

(b) (4) All the responses to deficiencies from Review #1 are found acceptable except the compatibility study. PMCs are proposed to provide the compatibility study reports with each (b) (4) The applicant agreed with the PMCs # (b) (4)-1 and # (b) (4)-2 on 3/4/2020.

1. Post Marketing Commitment # (b) (4)-1: Provide the compatibility study reports of the bulk solution statically contacting with each (b) (4) component (b) (4) for 24 hours. Establish a control strategy ((b) (4) to mitigate the risks from the incompatibility of the (b) (4) components (b) (4) . (b) (4)

Final protocol submission date: May 15, 2020; study completion: August 15, 2020; and final report submission: October 15, 2020.

2. Post Marketing Commitment # (b) (4)-2: We note that you are (b) (4) (b) (4) Establish a procedure which ensures that bulk solution (b) (4) update the master batch record accordingly.
Final protocol submission date: May 15, 2020; study completion: August 15, 2020; and final report submission: October 15, 2020.

A pre-approval inspection was performed for the drug substance Fluorescein Sodium manufacturing facility (b) (4) ended on (b) (4) the final classification of the inspection is VAI. All the other facilities are acceptable based on the profile. Therefore, the overall recommendation of "Approve" was entered for the NDA into Panorama by OPMA on 2/27/2020.

Biopharmaceutics: Adequate

No new biopharmaceutics information is submitted in the resubmission. Refer to the biopharmaceutics review # 1.

Microbiology (if applicable): Adequate

The applicant has provided adequate sterility assurance. The process is (b) (4) The sterilization of the (b) (4)

(b) (4) and the dropper are found acceptable in this resubmission.

C. Risk Assessment

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Eval.	Lifecycle Considerations
Sterility	Formulation Container closure Process parameters Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Endotoxin Pyrogen	Formulation Container closure Process parameters Scale/equipment	L		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	

			(b) (4)		
pH	Formulation Container closure Process parameters Scale/equipment	L		L	
Particulate matter	Formulation Container closure Process parameters Scale/equipment	M		L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

NA

5. Manufacturing Deficiencies

PMCs in section B

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies (Specify discipline, such as Environmental)

NA

Application Technical Lead Name and Date: Chunchun Zhang, Ph.D., 3/4/2020

QUALITY ASSESSMENT

MICROBIOLOGY

Product Background:

NDA: 211039

Drug Product Name / Strength: Fluorescein Sodium, (b) (4)% and Benoxinate Hydrochloride, 0.4%, Ophthalmic Solution

Route of Administration: Topical ophthalmic

Applicant Name: Valeant Pharmaceuticals Ireland

Manufacturing Site: Siegfried-Irvine
9342 Jeronimo Road
Irvine CA 92618

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

List Submissions Being Reviewed: Amendment 18 February 2020, Resubmission 16 December 2019, 22 January 2020 (labeling)

Highlight Key Outstanding Issues from Last Cycle: No information was provided in regard to sterilization of the (b) (4) and additional information was required for sterilization of the dropper.

Remarks: Amendment #15 was submitted in response to the Agency's Complete Response Letter (CRL) dated 19 July 2019. The response was received 16 December 2019 for deficiencies identified in product quality microbiology. The deficiencies agreed upon by the Division of Microbiology Assessment (DMA) differed from those sent to the applicant in the CRL. For the purpose of this review, the deficiencies that differed from those approved by DMA are provided as ***[Deficiency DMA approved/agreed]*** and those sent in the CRL as **[Deficeincy sent to the Applicant].** Some tables in this review have been adapted from the current submission. The RLD is NDA 208582 Altafluor Benox.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: N211039MR01.doc

List Number of Comparability Protocols (ANDA only): N/A

Product Quality Microbiology Assessment

For the purpose of this review, only those instances where the change in the deficiency language was either major or changed the semantics of the information request are indicated below in **[bold]**. The deficiencies are italicized and the responses to the deficiencies are reviewed below. In addition, the responses to an information request sent on 03 February 2020 were reviewed below.

(b) (4)

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(b) (4) This information was reviewed and deemed adequate from a product quality microbiology perspective in N211039MR01.doc.

List of Deficiencies: *None.*

Primary Microbiology Reviewer Name and Date:
Valerie A. Huse, Ph.D. *02/21/2020*

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Yeissa Chabrier-Roselló, Ph.D. *02/21/2020*

Valerie Huse

Digitally signed by Valerie Huse
Date: 2/21/2020 08:59:43AM
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Yeissa Chabrier Rosello

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Date: 2/21/2020 09:48:34AM
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/s/

CHUNCHUN N ZHANG
03/04/2020 01:01:13 PM

Recommendation: Complete Response

NDA 211039
Review # 1
June 11, 2019

Drug Name/Dosage Form	***Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution***
Strength	(b) (4) %/0.4%
Route of Administration	*Topical ophthalmic*
Rx/OTC Dispensed	*Rx*
Applicant	*Valeant Pharmaceuticals Ireland*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*9/24/2018*
Amendment	*12/14/2018*
Amendment	*2/4/2019*
Amendment	*2/19/2019*
Amendment	*3/15/2019*
Amendment	*4/4/2019*
Amendment	*4/5/2019*
Amendment	*5/13/2019*
Amendment	*5/24/2019*
Amendment	*6/4/2019*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Hari Sarker	Hari Sarker
Drug Product	Peter Guerrieri	Chunchun Zhang
Microbiology	Valerie Huse	Yeissa ChabrierRosello
Biopharmaceutics	Akm Khairuzzaman	Jing Li
Process	Feiyan Jin	Daniel Obrzut
Facility	Feiyan Jin	Daniel Obrzut
Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Peter Guerrieri	Chunchun Zhang

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	5/28/2019	LoA: 9/17/2018 Reviewed by Hari Sarker
	Tyoe II			Adequate	6/7/2019	LoA: 6/22/2018 Reviewed by Hari Sarker
	Type III			NA		LoA: 4/27/2018
	Type III			NA		LoA: 3/27/2018
	Type III			NA		LoA: 3/26/2018
	Type III			NA		LoA: 3/26/2018
	Type III			NA		LoA: 7/24/2018

[1]NA (There is enough data in the application, therefore the DMF did not need to be reviewed).

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	131170	

2. CONSULTS

NA

Executive Summary

I. Recommendations and Conclusion on Approvability

Satisfactory information and responses have been submitted to support drug substance, drug product, and biopharmaceutics aspects.

The drug substance Fluorescein Sodium facility [redacted] (b) (4) was recommended for a follow-up PAI inspection due to [redacted] (b) (4) issue. The requested PAI inspection was conducted on [redacted] (b) and was classified as OAI. All the other facilities are acceptable based on the profile. Therefore, the overall recommendation of "withhold" was entered for the NDA into Panorama by OPF on 6/5/2019. Additionally, two outstanding deficiencies from the manufacturing process are identified. Quality microbiology reviewer Dr. Valerie Huse has identified several outstanding deficiencies related to [redacted] (b) (4) [redacted] (b) (4) In agreement with the above recommendations, NDA 211039 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 discussion.

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

Facility comment:

1. *During a recent inspection of* [redacted] (b) (4) *manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.*

Manufacturing process comment:

2. *We acknowledge your responses dated June 4, 2019. However, you did not provide the data requested for the two process deficiencies we sent to you on May 22, 2019. We remind you that process validation is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected (Guidance for Industry Process Validation: General Principles and Practices (2011)),* [redacted] (b) (4)

[redacted] *Provide data to resolve the two process deficiencies we sent to you on May 22, 2019.*

1) *Provide the compatibility data of the bulk solution with the* [redacted] *to demonstrate that there are no significant changes in the physicochemical properties* [redacted] *of the drug product* [redacted]
2) *Provide the study report to establish the control strategy for* [redacted]. *In addition, update the master batch record with the* [redacted] *control strategy.*

Quality microbiology comment:

3. *The information request responses received by the Agency on 24 May 2019 stated that the* [redacted] *Alternately, provide a Letter of Authorization (LOA) granting access to a Drug Master File (DMF) that includes the location in the DMF where the relevant information can be found.*
4. *The Agency acknowledges the validation information and data provided for* [redacted]

   a) *Provide a description of the* [redacted]

   b) *It is unclear how the information for the* [redacted]

5. *Explain if the dropper with all of its components (the rubber dropper bulb, glass pipette and polypropylene closure included in Module 3.2.P.7 document "Dropper Bulb Drawing")* [redacted]

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	to be used for procedures requiring a disclosing agent in combination with topical ophthalmic anesthetic.
Duration of Treatment	Instill 1 to 2 drops topically in the eye as needed to achieve adequate anesthesia. See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance, Fluorescein Sodium, is an orange-red powder. The drug substance referenced in DMF (b) (4) was found adequate by Hari Sarker on 5/28/2019.
The drug substance, Benoxinate Hydrochloride, is referenced in DMF (b) (4) and was found to be adequate by Hari Sarker on 6/7/2019.

ii. Drug Product Quality Summary

Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, (b) (4) %/0.4% is a sterile and preserved ophthalmic solution and packaged into 6cc Type (b) amber glass vials (5mL fill volume) with a polypropylene cap/ (b) (4) and then the filled vial is labeled and placed into a unit carton. A sterile dropper is included for administration of the drug product to the eye.

Fluorescein Sodium and Benoxinate Hydrochloride ophthalmic solution, 0.25%/0.4% has been a marketed but unapproved product since 1994. (b) (4) (b) (4) Fluorescein Sodium (b) (4), Benoxinate Hydrochloride (b) (4) and preservative chlorobutanol (b) (4) are present in the formulation. (b) (4) All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. Chlorobutanol is the preservative in the formulation. The drug product specification includes tests for appearance, identity, assay, impurities (specified, unspecified and total), chlorobutanol assay, pH, osmolality, sterility, particulate matter and antimicrobial effectiveness testing. All analytical methods are described in reasonable detail and have been adequately validated. The applicant has performed extractable and leachable studies, no reportable extractable or leachable was detected. A risk assessment on the elemental impurity was performed and indicate the results are lower than PDE per Q3D and USP <232>.

The applicant has submitted three registration batches which are filled at the (b) (4) commercial scale using the commercial process and packaging at the commercial site. Data through nine months at long term 5°C and six months at accelerated condition 25°C/40% RH at the horizontal orientation are provided. The applicant also provided twenty-one months of three supportive stability batches at 5°C and six months of data at 25ºC/ 40% manufactured at the previous commercial site, Bausch & Lomb, Tampa, FL. Additionally, the applicant has performed one month in-use stability at 25°C/ 60% once the dropper replaced (b) (4) All the quality attributes remain within the proposed specifications. Photostability

study has suggested the proposed product is sensitive to light, a caution statement is proposed to be included in the labeling. Therefore, the expiration date of 21 months is granted when stored at 2 °C- 8 °C; the in-use shelf life of 30 days at room temperature is adequately supported.

The storage statement is "Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light. May be stored at room temperature for up to one month." and will be finalized at the OND's labeling meeting.

The proposed drug product manufacturing process consists: (b) (4) During the NDA review several information requests regarding (b) (4) were conveyed to and addressed by the applicant. However, the applicant hasn't provided adequate response to the two outstanding deficiencies as shown below, therefore, this NDA is not recommended for approval from the manufacturing process perspective.

We acknowledge your responses dated June 4, 2019. However, you did not provide the data requested for the two process deficiencies we sent to you on May 22, 2019. We remind you that process validation is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected (Guidance for Industry Process Validation: General Principles and Practices (2011)), (b) (4) (b) (4) Provide data to resolve the two process deficiencies we sent to you on May 22, 2019.

1. *Provide the compatibility data of the bulk solution with the (b) (4) to demonstrate that there are no significant changes in the physicochemical properties (b) (4)*
2. *Provide the study report to establish the control strategy (b) (4)*

The drug product is a (b) (4). The quality microbiology reviewer Dr. Valerie Huse has identified several outstanding deficiencies including (b) (4) (b) (4) Therefore, NDA 211039 is found inadequate from quality microbiology perspective.

1. *The information request responses received by the Agency on 24 May 2019 stated that the (b) (4) (b) (4)*

(b) (4)

(b) (4) *Alternately, provide a Letter of Authorization (LOA) granting access to a Drug Master File (DMF) that includes the location in the DMF where the relevant information can be found.*

2. *The Agency acknowledges the validation information and data provided for* (b) (4)

(b) (4)

3. *Explain if the dropper* (b) (4)

(b) (4)

(b) (4)

4. *Provide the following information, if applicable, for validation of the*

(b) (4)

(b) (4)

Biopharmaceutics reviewer Dr. Akm Khairuzzaman has found the "bridge" between the proposed and the listed drug product acceptable and a biowaiver is not feasible for the proposed drug product.

OPF has issued a withhold recommendation for the drug substance manufacturing site (b) (4) from the outcome of the recent inspection ending (b) (4) All the other facilities are acceptable based on the profile. Therefore, the overall recommendation of "withhold" was entered for the NDA into Panorama by OPF on 6/5/2019.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.

Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	**L**	(b) (4)	**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		L	

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

This NDA is recommended for Complete Response from the Product Quality Perspective.

On behalf of the OPQ team
Chunchun Zhang, Ph.D. ATL for NDA 211039

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BIOPHARMACEUTICS

Product Background: .

NDA: 211039

Drug Product Name / Strength: Fluorescein Sodium (b) (4)% and Benoxinate Hydrochloride 0.4% Ophthalmic Solution (sterile, supplied as 5 mL in 6 cc bottle)

Route of Administration: Ophthalmic

Indication: For procedures requiring a disclosing agent in combination with topical ophthalmic anesthetic

Applicant Name: Valeant Pharmaceuticals Ireland

List of Submissions being reviewed: original submission (seq # 0000) dated 09/24/2018

Review Summary: This is a sterile ophthalmic solution product submitted through 505 b(2) pathway. Dissolution is not relevant for this solution product. This Biopharmaceutics review is focused on evaluation of the request to waive the in vivo bioavailability studies. Due to the composition differences between the proposed drug product and the listed drug product, a biowaiver under regulation 21 CFR 320.22(b)(1) is not feasible for the proposed drug product. However, the "bridge" between the proposed and the listed drug product is supported by the provided data/ information, based on 21 CFR 320.24(b)(6).

Review Recommendation: **Adequate**

From the Biopharmaceutics perspective, NDA 211039 for Fluorescein Sodium (b) (4)% and Benoxinate Hydrochloride 0.4% Ophthalmic Solution, is recommended for APPROVAL.

Assessment of Information/ Data Supporting Bridging of Formulations: Acceptable.

The formulation of the proposed drug product is not qualitatively and quantitatively the same as the formulation of the listed drug product, therefore, a biowaiver under regulation 21 CFR 320.22(b)(1) is not feasible for the proposed drug product. However, the "bridge" between the proposed and the listed drug product is supported by the provided data, based on 21 CFR 320.24(b)(6), that justifies the differences in drug products would not contribute to differences in the in vivo performance. In addition, The proposed drug product has been used in clinical since 1993 which further supported the

efficacy and safety of the proposed drug product. Refer to the Clinical Review for further details.

The applicant previously submitted a controlled correspondence to OGD on March 5, 2018, requesting evaluation of for Q1/Q2 sameness to the RLD (Altafluor Benox, NDA-208582). However, OGD confirmed that the formulation is not qualitatively the same as that of the RLD product, and therefore a biowaiver was not granted as per 21 CFR 320.22 (b)(1).

The Applicant submitted this NDA through 505 b(2) regulatory pathway and requested a waiver of in vivo BA/BE based on literature citation. The submitted literature citations are subject to review by the clinical division. The proposed drug product that is the subject of this NDA is the same as that previously marketed by Bausch& Lomb as a USP compendial unapproved drug product.

The Applicant selected NDA 208582 as the listed drug product as per Clinical Reviewer's request. The following shows the formulation composition of the proposed drug product in comparison to that of the listed drug product.

NDA-211039

Component	Formulation Quantity	Function	Quality Standard
Fluorescein Sodium[1]	(b) (4)	Active Ingredient	USP
Benoxinate Hydrochloride[1]	0.4%[3]	Active Ingredient	USP
Chlorobutanol	(b) (4)	Antimicrobial preservative	NF
Boric Acid	(b) (4)		NF
Povidone			USP
Hydrochloric Acid	(b) (4)	pH adjustment	NF
Water for Injection (WFI)	(b) (4)		USP
			(b) (4)

NF = National Formulary USP = United States Pharmacopeia Q.S. = Quantity Sufficient

Listed Product (NDA-208582) (not FOIable)

mg/mL	Ingredients	CAS #	Percentage
2.2 (b) (4)	Fluorescein USP	(b) (4)	(b) (4)
(b) (4)	Sodium Hydroxide NF		
4.00	Benoxinatae Hydrochloride USP		0.4%
11.00	Chlorobutanol NF		(b) (4)
(b) (4)	Povidone (b) (4)		
	Hydrochloric Acid (b) (4)		
	Boric Acid NF		
	Water for Injection USP		-
Qs	May contain Hydrochloric Acid and/or Sodium Hydroxide to adjust a target pH of (b) (4)		-

The two formulations differ in the buffering system, though they have same pH range in the final drug product (pH 4.3 – 5.3 as per Drug Product Specification (proprietary information)). The difference in buffering system is not expected to impact the disposition of the drug product at the local site.

Osmolality of the LD product is 270 – 330 mOsm/kg, while proposed drug product has a proposed range of 290 - 404 mOsm/kg. Difference in osmolality is not expected to alter disposition of the drug in vivo. The osmolality of both products falls within the range of patients tolerance, hence the difference does not raise additional safety/ patients compliance concern.

Overall, due to the composition differences between the proposed drug product and the listed drug product, a biowaiver under regulation 21 CFR 320.22(b)(1) is not feasible for the proposed drug product. However, the "bridge" between the proposed and the listed

drug product is supported by the provided data/ information, based on 21 CFR 320.24(b)(6). In addition, the longtime clinical use of the proposed drug product as an un-approved marketed product and literature reports further support the efficacy and safety of the proposed drug product (Refer to the Clinical Review for further details).

From the Biopharmaceutics perspective, NDA 211039 for Fluorescein Sodium (b) (4)% and Benoxinate Hydrochloride 0.4% Ophthalmic Solution, is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Akm Khairuzzaman, Ph.D., 4/25/2019

Secondary Reviewer Name and Date : Jing Li, Ph.D., 4/25/2019

Akm Khairuzzaman

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Date: 4/26/2019 02:26:17PM
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Jing Li

Digitally signed by Jing Li
Date: 4/26/2019 03:02:03PM
GUID: 508da7420002bb05ac913303b23c39bb

MICROBIOLOGY

Product Background:

NDA: 211039

Drug Product Name / Strength: Fluorescein Sodium, (b) (4)% and Benoxinate Hydrochloride, 0.4%, Ophthalmic Solution

Route of Administration: Topical ophthalmic

Applicant Name: Valeant Pharmaceuticals Ireland

Manufacturing Site: Siegfried-Irvine
9342 Jeronimo Road
Irvine CA 92618

Method of Sterilization: (b) (4)

Review Recommendation: **Inadequate- Major**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

List Submissions Being Reviewed: Original 24 September 2018, 05 April 2019, 24 May 2019 (IR response)

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The drug product is indicated for procedures requiring a disclosing agent in combination with topical ophthalmic anesthetic and it can also be used for minor operations of the eye. Some tables in this review have been adapted from the current submission. The RLD is NDA 208582 Altafluor Benox.

Concise Description Outstanding Issues Remaining: No information was provided in regard to sterilization of (b) (4) and additional information is required for validation of the sterile dropper. See last page for deficiency.

Supporting Documents: None.

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

The drug substance is not provided sterile. Therefore, the product quality microbiology of the drug substance is not reviewed.

P.1 Description of the Composition of the Drug Product

(1.14.1.3 Draft Labeling Text)
(3.2.P.2 Components of the Drug Product)
(3.2.P.7.1 Primary Container Closure)
(3.2.P.7.2 Secondary Container Closure)

- **Description of drug product –** Sterile, preserved and multi-dose aqueous ophthalmic solution supplied in a 6cc glass vial with a 20 mm polypropylene cap and 5 mL fill. The drug product is packaged as a kit with a sterile rubber dropper bulb and glass pipette.

- **Drug product composition –**

Ingredient	Quantity	Function
Fluorescein Sodium	(b) (4)%	Active Ingredient
Benoxinate Hydrochloride	0.4%	Active Ingredient
Chlorobutanol	(b) (4)	Antimicrobial preservative
Boric Acid		(b) (4)
Povidone		
Hydrochloric Acid	(b) (4)	pH adjustment
Water for Injection (WFI)	(b) (4)	(b) (4)

- **Description of container closure system –**

Component	Description	Manufacturer
Bottle (b) (4)	6 cc amber glass vial, (b) (4)	(b) (4)
Closure (b) (4)	20 mm black cap, polypropylene (b) (4)	
Dropper bulb (provided separate from the DP container/closure system)	Glass (b) (4) (b) (4)	Not provided.

Adequate

Reviewer's Assessment: The description of the drug product composition and container/closure system meet regulatory expectations for a sterile, preserved and multi-dose drug product.

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Yeissa Chabrier Rosello

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Date: 6/07/2019 11:30:29AM
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Chunchun Zhang

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