CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208135Orig1s000

CHEMISTRY REVIEW(S)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208135	**Submission Type: 505(b)(2)**	**Established/Proper Name: Tetracaine hydrochloride**
Applicant: Alcon Research, Ltd	**Letter Date: April 30, 2015**	**Dosage Form: Sterile Ophthaimic Solution**
Chemical Type:	**Stamp Date: April 30, 2015**	**Strength: 0.5%**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		This NDA may be filed from the CMC perspective
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			None identified so far.
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			Two IR questions for Micro (please see Page 12)

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

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Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	Tetracaine hydrochloride
21.	End of Phase II/Pre-NDA Agreements		☐	☒	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other		☐	☒	
Quality Considerations					
26.	Drug Substance Overage		☒	☐	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☐	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	☐	To be determined during review
36.		Excipients	☐	☐	To be determined during review
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	To be determined during review
43.	Genotoxic Impurities or Structural Alerts		☐	☒	DS: None & DP: To be determined during review
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☐	The Applicant is requesting a waiver of the requirement to provide evidence of in vivo bioavailability for the drug product.
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☐	The Applicant is requesting a waiver of the requirement to provide evidence of in vivo bioavailability for the drug product.
49.	New product design[1]		☐	☒	
50.	Other		☐	☐	

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

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

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

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

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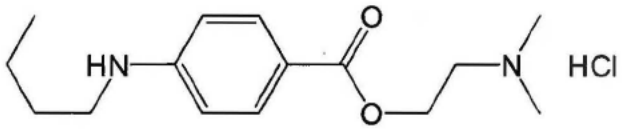
C. FILING CONSIDERATIONS					
	❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	The Applicant is requesting a waiver of the requirement to provide evidence of in vivo bioavailability for the drug product.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☒	☐	☐	The Applicant cited 21 CFR 320.22 (e) section for the biowaiver request.
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	

C. FILING CONSIDERATIONS					
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	☒	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☐	☐	☒	

Drug Substance:

Tetracaine HCl



Chemical Formula: $C_{15}H_{25}ClN_2O_2$
Molecular Weight: 300.82

Tetracaine HCl drug substance is a white crystalline powder, soluble in water. [redacted] Applicant refers to [redacted] DMF [redacted] (LOA provided). The DMF was last reviewed by [redacted] and found to be adequate. Since then two annual reports and one quality amendment/information submitted. The applicant provided specifications and batch data, however referred to the DMF for most of the information.

Drug Product:

Tetracaine HCl Ophthalmic Solution, 0.5%, Steri Units®

The drug product is a single use pre-sterilized ready-to-use topical anesthetic product for ocular use. Composition and batch formula provided with [redacted] All excipients are compendial.

Table 3.2.P.3.2–1 Batch Formula for a Typical [redacted] Batch of Tetracaine HCl Ophthalmic Solution, 0.5% FID 94152

Ingredient	% w/v	Quantity (g) per [redacted] Batch	Quality Standard
Tetracaine Hydrochloride	0.5	[redacted]	USP
Sodium Acetate Trihydrate	[redacted]		USP
Sodium Chloride			USP
[redacted] Acetic Acid	Adjust pH to approximately 4.5	Adjust pH to approximately 4.5	USP NF
Water for Injection	[redacted]		USP

Manufacturers:

DP manufacturing and testing:

Alcon Research, Ltd. (subsidiary of Alcon Laboratories, Inc.)

(b) (4)

LOA for all the DMFs provided.

Manufacturing description provided. Temperature controlled to (b) (4)

Specifications for DP:

Table 3.2.P.5.1–1 Regulatory Acceptance Specifications for Tetracaine Hydrochloride Ophthalmic Solution, 0.5% (FID 94152)

Test	Specification
Tetracaine Hydrochloride Identity (HPLC) [a]	Positive
Tetracaine Hydrochloride Identity (TLC) [a]	Positive
Tetracaine Hydrochloride Assay (HPLC)	90 to 110% Label
Tetracaine Hydrochloride Impurities (HPLC) [b] (b) (4) Any Single Unspecified Impurity [c] Total Impurities	NMT (b) (4)% of Active (b) (4)% of Active NMT (b) (4)% of Active NMT %% of Active NMT %% of Active NMT (b) (4)% of Active
pH (Potentiometric)	3.7 – 5.5
Osmolality (Freezing Point Depression)	(b) (4) mOsm/kg
Appearance (Visual): Color Clarity Precipitate	(b) (4) NMT Ph. Eur. II None
Particulate Matter by HIAC	Meets USP Requirements NMT (b) (4) particles/ml (b) (4) NMT particles/mL NMT particles/mL
Sterility [d]	Meets USP Requirements

[a] Release Test only
[b] Report any impurity ≥ (b) (4)% of active
[c] (b) (4) are included under Any Single Unspecified Impurity.
[d] Sterility testing will not be routinely conducted on production lots except at release. However, if tested, samples will comply with USP requirements.
NMT = Not more than

The drug product specifications includes two ID tests, however, the ID by TLC needs to be verified. The retention time for DP seems to match that of the vehicle.

Batch data for (b) (4) batches (b) (4) provided. No OOS result noted.

The applicant provided a list of potential impurities and degradants. None with apparent structure alert components are noted. The proposed impurity specifications are high. The reviewer should confirm with the pharm-tox reviewer if the proposed specifications for the impurity are acceptable given the strength and the dosage.

Container Closure: MDPE round bottle with LDPE dispensing plug and polypropylene closure. Dropsize evaluation provided. Sterility, CC integrity, and bacterial endotoxin information provided.

Stability data:

52 weeks for longterm (25°C/40%RH and 5°C/35%RH), 26 weeks accelerated (40°C/<25%RH), 6 weeks light, and 1 week freeze thaw cycle provided.

Table 3.2.P.8.1–3 Pull Schedules and Storage Conditions of Tetracaine Hydrochloride Ophthalmic Solution 0.5%

Storage Condition [b]	Temperature (°C)	Relative Humidity (%)	Period (Weeks)
Initial	N/A		0
Accelerated	40	NMT 25	13, 26
Intermediate	30	65	52, 78, 104[c]
Room temperature	25	40	13, 26, 39, 52, 78, 104
Refrigerated	5	35	26, 52, 104
Freeze/Thaw Cycle [d]	-20 / 30	No Humidity Control	1
Light Cabinet/ Secondary Packaging [e]	25	40	6
Light Cabinet [e]	25	40	6

[a] The stability protocol has been designed to meet ICH requirements.
[b] Samples for all storage conditions are stored in the horizontal orientation.
[c] For the 30°C/65% RH storage condition, samples were initially "store only". Stability study was initiated as per ICH guidelines from 52 weeks onward due to > 5% change in the assay results of tetracaine hydrochloride at 26 weeks for 40°C.
[d] A cycle is defined as 28 hours at -20°C followed by 28 hours at 30°C; analysis is performed at the end of the third cycle only. Tested for lot 18956-01 only.
[e] Light Cabinet with minimum 1.2 million lux hours (Visible) and 200 watt hours meter^2 (UV) Tested for lot 18956-01 only.

Initial Risk Assessment:

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

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Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
		• (b) (4)						
Assay (preservative)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Lack of effectiveness through shelf-life	1 (Release) 1 (Stability)	1	1	1	No preservative. Single use.	L
Assay (anti-oxidant)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Decrease in potency						L
Uniformity of Dose (Fill Volume/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Insufficient dose	2	2	2	8	Applicant checks and records fill volume at frequent intervals.	L
Osmolality	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Irritation • Edema	2	2	2	8	Osmolality testing is performed (DP specifications).	M
pH-	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Irritation • Particulate formation due to (b) (4) (with high pH)	2	2	2	8	Testing is performed (DP specifications)	L
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Irritation • Embolism	3	5	2	30	Tested in DP specifications.	M
Leachable extractables	• Formulation	• Generation of						

Product Property/Impact of Change/CQA	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	RPN	Comment	Risk
	• Container closure • Process parameters • Scale/equipment • Site	impurities	4	4	3	48		M
Appearance (Color/turbidity)	• Formulation • Container closure • Process parameters • Scale/equipment • Site		3	3	1			L

Microbiology deficiencies identified at this time, that are to be conveyed to the applicant.

1. With regard to method suitability testing for the sterility test; to be performed at release of the finished drug product, it is acknowledged that a supplemental report is provided for testing with *A. niger*. Please provide the initial method suitability testing report that includes the other compendial organisms.

2. The regulatory specification provided in 3.2.P.5.1 indicates that the sterility test is to be performed for commercial production lots at release only. 3.2.P.8.2 page 1 of 2 states that sterility testing will be performed at expiry and beyond for primary stability batches. For commercial lots placed in the stability program post-approval, please clarify if the sterility test is performed at release as well as at expiry and beyond as part of the stability program.

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2015.06.30 09:06:48 -04'00'

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBYN S JORDON
03/09/2016

Recommendation:
Approval

NDA 208135
Review #1 Addendum

Drug Name/Dosage Form	STERI UNITS® /ophthalmic solution
Strength	0.5%
Route of Administration	Ophthalmic solution
Rx/OTC Dispensed	Rx
Applicant	Alcon Research, Ltd.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gene Holbert	Branch I/DNDAPI/ONDP
Drug Product	Milton Sloan	Branch III/DNDP I/ONDP
Process	Vidya Pai	Branch VII/DPA/OPF
Microbiology	Lisa Shelton	Branch II/DMA/OPF
Facility	Vidya Pai	Branch VII/DPA/OPF
Biopharmaceutics	Banu Zolnik	Branch I/DBP/ONDP
Regulatory Business Process Manager	Navi Bhandari	
Application Technical Lead	Anamitro Banerjee	Branch II/DNDP I/ONDP
Laboratory (OTR)		
ORA Lead	Paul Perdue Jr.	
Environmental Assessment (EA)		

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for APPROVAL from the CMC perspective. As discussed in detail elsewhere in this review, we had extensive correspondence with Alcon on the similarity of the currently marketed and the to-be-marketed products, specifically from the standpoint of impurities. Based on the information provided by Alcon (which includes a drop in assay due to [redacted] (b) (4) qualitative analysis of the marketed products from 2013, an assessment of the critical factors during the manufacturing process which impact the level of the impurities, and that the formulation, the manufacturing process, or container closure remains unchanged over the years), it seems that the impurities reported in the registration batches were present in the marketed products although quantitative data is limited. To gain further confidence of the impurity levels and the analytical method described to evaluate the impurities, we are seeking the FDA laboratory in St. Louis to verify the method. The facilities are currently acceptable. The proposed labeling is acceptable from the CMC point of view.

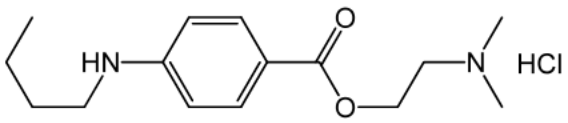
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

1. Chemical Name or IUPAC Name/Structure



IUPAC Name: 2-(dimethylamino)ethyl 4-(butylamino)benzoate hydrochloride
Chemical Formula: $C_{15}H_{25}ClN_2O_2$
Molecular Weight: 300.82

2. Properties/CQAs Relevant to Drug Product Quality

Stability at pH 3.7 – 5.5

3. List of starting materials

[redacted] (b) (4)

4. Suppliers of starting materials (site)

The information is provided in the DMF (b) (4). This DMF was last reviewed in July 17, 2015 and found to be adequate. No quality amendment has since been submitted.

5. Summary of Synthesis

A description of the synthesis is provided in the DMF (b) (4). This DMF is currently adequate. The tetracaine HCl drug substance and the impurities are described and characterized in the DMF. The drug substance specifications meet the USP monograph with additional tests for related substances that are consistent with the Ph.Eur. Compendial methods are used to test the drug substance.

6. Container Closure

The drug substance is stored (b) (4).

7. Retest Period & Storage Conditions

The tetracaine HCl drug substance is stored at (b) (4) retest period. Stability data for the tetracaine HCl drug substance is provided in the DMF (b) (4). The DMF is currently adequate.

B. Drug Product [Established Name] Quality Summary

1. Strength

The drug product is a 0.5% sterile ophthalmic solution.

2. Description/Commercial Image

The drug product is a (b) (4) sterile ophthalmic solution filled in a natural medium density (b) (4) round bottle with an LDPE dispensing plug and a white polypropylene closure enclosed in a PVC blister with a heat sealed Tyvek backing.

3. Summary of Product Design

Tetracaine HCl Ophthalmic Solution 0.5% has been marketed in the US since 1959. Tertacaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNITS® has been manufactured and marketed by Alcon for over 20 years and is a pre-DESI grandfathered product. With this submission, the applicant is seeking formal approval of the drug for its historic medical application in ophthalmological setting and assumes all of the regulatory obligations of an approved NDA. This product is a single use sterile product with no preservative.

4. List of Excipients:

Apart from the drug substance, the drug product contains sodium acetate trihydrate (b) (4) (b) (4), sodium chloride (b) (4), acetic acid (b) (4)/pH adjuster), and Water for Injection (b) (4). All the excipients are of USP/NF grade. No novel excipients or excipients of human or animal origin are used.

5. Process Selection (Unit Operations Summary)

The manufacturing process follows (b) (4)

(b) (4)

Applicant has indicated that the process proposed in the NDA is identical to the process used to manufacture the currently marketed product by providing the change control history for the last 10 years. The list of changes to the manufacturing process since 1999 indicates ***that the quality attributes (specifically impurity profile and assay) in the historically marketed product is*** (b) (4) ***to the proposed*** product. The individual change in assay, for over (b) (4) (since Jan 2010) was tracked and presented in an I-chart, showing an approximate drop of (b) (4)% across the (b) (4) It appears that the existing and intended overage ((b) (4)%), has tracked the drop in assay.

6. Container Closure

The container closure is comprised of natural medium density polyethylene ((b) (4) (b) (4)) in 4 mL round bottle with a natural LDPE dispensing plug and a white polypropylene closure enclosed in a PVC blister with heat sealed Tyvek backing. The bottle and plug components (b) (4) and the closure is (b) (4).

7. Expiration Date & Storage Conditions

The stability data provided by the applicant supports the requested shelf life of 104 weeks (24 months) when the product is stored between 2 – 25°C in the proposed container closure.

8. List of co-packaged components

None.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	STERI UNITS®
Non Proprietary Name of the Drug Product	Tetracaine Hydrochloride 0.5% Ophthalmic Solution
Non Proprietary Name of the Drug Substance	Tetracaine hydrochloride
Proposed Indication(s) including Intended Patient Population	For procedures in which a rapid and short-acting topical ophthalmic anesthetic is indicated
Duration of Treatment	One drop topically in the eye(s) as needed
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation:
   - Drug Substance:

Tetracaine hydrochloride is soluble in water. However no information is provided about the BCS classification.

- Drug Product:
  Since the proposed drug product is an ophthalmic solution, BCS classification is not applicable.

2. Biowaivers/Biostudies
   - Biowaiver Requests

The Applicant requested a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data on the basis of compatibility with public health due to its long history of clinical safety and effectiveness.

The proposed drug product will be administered one drop in the eye. It is stated in the label that tetracaine HCL is rapidly metabolized by plasma esterases in ocular tissues limiting distribution to ocular tissues and limiting any systemic absorption. Therefore, the biowaiver request is granted.

- PK studies

The Applicant did not conduct any PK studies.

- IVIVC

The proposed drug product is an ophthalmic solution, therefore IVIVC is not applicable.

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Environmental Assessment

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b). The claim was reviewed and found to be acceptable.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2016.02.26 10:05:41 -05'00'

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ASSESSMENT OF THE FACILITIES

NA

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

NA

ASSESSMENT OF MICROBIOLOGY

NA

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant requested a categorical exclusion for environmental assessment under 21 CFR 25.31(b) for "action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb)."
The calculation provided by the applicant shows an expected introduction concentration (EIC) of (b) (4).

Reviewer's Assessment:

Acceptable

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
Adequate
Anamitro Banerjee/ONDP/DNDP I February 24, 2016

Secondary Review Comments and Concurrence:

I agree with Dr. Banerjee's recommendation.
Balajee Shanmugam/ONDP/DNDP 1
February 25, 2016

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

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
Labeling recommendations are ongoing and have not been finalized. Labeling concerns have been conveyed to OND for consideration during labeling negotiations.

Milton J. Sloan, Ph.D.
Feb. 25, 2016

Secondary Review Comments and Concurrence:

I concur with the recommendations.

Balajee Shanmugam, Ph.D.
February 25, 2016

II. List of Deficiencies To Be Communicated

None

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Initial Risk Ranking***	**Justification**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments****
	H, M, or L			Acceptable or Not Acceptable	
Assay (API), stability	L	The applicant refers to the DMF (b) (4). This DMF is currently adequate	No change	Acceptable	None

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
		H, M, or L		Acceptable or Not Acceptable	
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H	Process conducted at commercial scale. Drug product manufacturer and (b) (4) (b) (4) Blister pack acceptable.		Changes to (b) (4) (b) (4) protocol for Blister packs to consider impact on (b) (4) impurities
Endotoxin Pyrogen	• Formulation • Container closure	M	Not applicable for this product	Acceptable	NA

	• Process parameters • Scale/equipment • Site		as this a short acting topical ophthalmic anesthetic.		
Assay (API), stability	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	N/A		
Assay (preservative)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	N/A		
Assay (antioxidant)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	N/A		
Uniformity of Dose (Fill Volume/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	N/A		
Osmolality	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	N/A		
pH	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	N/A		Changes to formulation pH to consider impact on impurities
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M	(b) (4)	Acceptable	NA
Leachable extractables	• Formulation • Container closure	M		Acceptable	NA

	• Process parameters • Scale/equipment • Site		studies included.		
Appearance (Color/turbidity)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L	N/A		
Tetracaine Hydrochloride Assay and Impurities	Potentially unqualified impurity levels of (b) (4)	M	Requested MV for assay and impurity method	Acceptable	Note MV recommendation and comments

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

Recommendation:
Approval pending resolution of impurity levels from the Pharmtox and clinical perspectives.

NDA 208135
Review #1

Drug Name/Dosage Form	STERI UNITS® /ophthalmic solution
Strength	0.5%
Route of Administration	Ophthalmic solution
Rx/OTC Dispensed	Rx
Applicant	Alcon Research, Ltd.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gene Holbert	
Drug Product	Milton Sloan	
Process	Vidya Pai	Branch VII/DPA
Microbiology	Lisa Shelton	Branch II/DMA
Facility	Vidya Pai	Branch VII/DPA
Biopharmaceutics	Banu Zolnik	Branch I/DBP
Regulatory Business Process Manager	Navi Bhandari	
Application Technical Lead	Anamitro Banerjee	Branch II/ONDP
Laboratory (OTR)		
ORA Lead	Paul Perdue Jr.	
Environmental Assessment (EA)		

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)	(b) (4)	Adequate	07/17/2015	
	Type III					
	Type III					
	Type III					
	Type V					N/A[1]
	Type V					N/A[1]

[1] N/A. From a product quality microbiology standpoint, there is enough data in the application; therefore, the DMF does not need to be reviewed.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	115866	

2. CONSULTS:

No consults requested.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for APPROVAL from the CMC perspective pending resolution of the impurity levels in the drug product specifications from the clinical and pharmtox perspective.

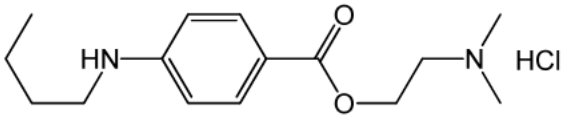
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

1. Chemical Name or IUPAC Name/Structure



IUPAC Name: 2-(dimethylamino)ethyl 4-(butylamino)benzoate hydrochloride
Chemical Formula: $C_{15}H_{25}ClN_2O_2$
Molecular Weight: 300.82

2. Properties/CQAs Relevant to Drug Product Quality

Stability at pH 3.7 – 5.5

3. List of starting materials

(b) (4)

4. Suppliers of starting materials (site)

The information is provided in the DMF (b) (4). This DMF was last reviewed in July 17, 2015 and found to be adequate. No quality amendment has since been submitted.

5. Summary of Synthesis

A description of the synthesis is provided in the DMF (b) (4). This DMF is currently adequate. The tetracaine HCl drug substance and the impurities are described and characterized in the DMF. The drug substance specifications meet the USP monograph with additional tests for related substances that are consistent with the Ph.Eur. Compendial methods are used to test the drug substance.

6. Container Closure

The drug substance is stored in double polyethylene bag inside a fiber drum.

7. Retest Period & Storage Conditions

The Tetracaine HCl drug substance is stored at [redacted] retest period. Stability data for the Tetracaine HCl drug substance is provided in the DMF [redacted]. The DMF is currently adequate.

B. Drug Product [Established Name] Quality Summary

1. Strength

The drug product is a 0.5% pre-sterilized, ready-to-use ophthalmic solution.

2. Description/Commercial Image

The drug product is a [redacted] sterile ophthalmic solution filled in a natural medium density [redacted] round bottle with an LDPE dispensing plug and a white polypropylene closure enclosed in a PVC blister with a heat sealed Tyvek backing.

3. Summary of Product Design

Tetracaine HCl Ophthalmic Solution 0.5% has been marketed in the US since 1959. Tertacaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNITS® has been manufactured and marketed by Alcon for over 20 years and is a pre-DESI grandfathered product. With this submission, the applicant is seeking formal approval of the drug for its historic medical application in ophthalmological setting and assumes all of the regulatory obligations of an approved NDA.

This product is a single use sterile product with no preservative.

The drug product specifications include tests for two [redacted] that are controlled at NMT [redacted]% and [redacted]%. The total impurity, as a result is controlled at NMT [redacted]%. These limits are based on the batch release and stability data provided in the NDA. CMC consulted with Pharm/Tox on these impurities and Pharm/Tox reviewer confirmed that these impurities and the [redacted] are not qualified at the proposed limits. In their review, the Pharm/Tox deferred to CMC and clinical on the acceptability of the proposed limits. Upon repeated requests to provide impurity profile for historical commercial batches, the applicant indicated that these impurities and other [redacted] impurities were not tested in the past. The applicant indicated that no changes to the manufacturing process were made since 1996 (TCON dated January 21, 2016 and follow-up email dated January 22, 2016). Based on this information, it may be concluded that impurity profile in the proposed product will be the same or similar to the Tetracaine Hydrochloride Ophthalmic Solution 0.5% currently marketed by the applicant. ***However, the safety of the impurity at the proposed levels should be assessed by the clinical and nonclinical divisions***.

4. List of Excipients:

Apart from the drug substance, the drug product contains sodium acetate trihydrate [redacted], sodium chloride [redacted], acetic acid [redacted]/pH adjuster), and

Water for Injection (b) (4). All the excipients are of USP/NF grade. No novel excipients or excipients of human or animal origin are used.

5. Process Selection (Unit Operations Summary)

The manufacturing process follows (b) (4)

6. Container Closure

The container closure is comprised of natural medium density polyethylene (b) (4) (b) (4) in 4 mL round bottle with a natural LDPE dispensing plug and a white olypropylene closure enclosed in a PVC blister with heat sealed Tyvek backing. The bottle and plug components (b) (4) and the closure is (b) (4) sterilized.

7. Expiration Date & Storage Conditions

The stability data provided by the applicant supports the requested shelf life of 104 weeks (24 months) when the product is stored between 2 – 25°C in the proposed container closure.

8. List of co-packaged components

None.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	STERI UNITS®
Non Proprietary Name of the Drug Product	Tetracaine Hydrochloride 0.5% Ophthalmic Solution
Non Proprietary Name of the Drug Substance	Tetracaine hydrochloride
Proposed Indication(s) including Intended Patient Population	For procedures in which a rapid and short-acting topical ophthalmic anesthetic is indicated
Duration of Treatment	One drop topically in the eye(s) as needed
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation:
   - Drug Substance:

Tetracaine hydrochloride is soluble in water. However no information is provided about the BCS classification.

- Drug Product:
  Since the proposed drug product is an ophthalmic solution, BCS classification is not applicable.

2. Biowaivers/Biostudies
   - Biowaiver Requests

The Applicant requested a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data on the basis of compatibility with public health due to its long history of clinical safety and effectiveness.

The proposed drug product will be administered one drop in the eye. It is stated in the label that tetracaine HCL is rapidly metabolized by plasma esterases in ocular tissues limiting distribution to ocular tissues and limiting any systemic absorption. Therefore, the biowaiver request is granted.

- PK studies

The Applicant did not conduct any PK studies.

- IVIVC

The proposed drug product is an ophthalmic solution, therefore IVIVC is not applicable.

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

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

The proposed drug product is an ophthalmic solution; therefore, a dissolution test is not needed for assuring the drug product quality

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

N/A. The Applicant did not conduct any clinical study during development. The Applicant is requesting a biowaiver.

14.1. **Biowaiver Request**

The Biopharmaceutics review is focused on the evaluation of the overall information/data supporting the approvability of the biowaiver request.

This NDA is a 505(b)(2) application which relies solely on published literature to support the drug product's safety and efficacy. The Applicant stated that tetracaine hydrochloride was invented in 1932, and that Tetracaine Hydrochloride Ophthalmic Solution 0.5% has been legally marketed in the United States by this Applicant since 1959 and by other manufacturers with an FDA status of "unapproved drug. Tetracaine Hydrochloride Ophthalmic Solution 0.5% has been widely used as a local anesthetic when given by topical administration and local injections. Per 21 CFR 320.22 (e), the Applicant is requesting a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data on the basis of the protection of the public health (good cause) and its long history of clinical safety and effectiveness.

Reviewer's Assessment:

Tetracaine HCl is soluble in water. The proposed drug product will be administered by giving one drop in the eye. It is stated in the proposed label that tetracaine HCl is rapidly metabolized by plasma esterases in ocular tissues limiting its distribution to ocular tissues and limiting any systemic absorption. Several literature references supporting this claim are provided in the NDA. Because tetracaine cannot be easily measured and detected in the ocular tissue or systemic circulation, and based on the long history of clinical safety and effectiveness, the biowaiver request is granted.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From the Biopharmaceutics perspective, NDA 208135, Tetracaine HCl, ophthalmic solution 0.5% is recommended for **APPROVAL.**

1/12/16

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

Secondary Concurrence and Signature:
I concur with Dr. Sizanli Zolnik's assessment and recommendation.

1/12/16

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

ASSESSMENT OF MICROBIOLOGY

2.3.P DRUG PRODUCT

14. Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

Applicant's response: Information is provided as presented below.

Product Quality Microbiology Assessment

Notes to reviewer:

- The pertinent CTD sections are included below. Except where noted otherwise, all references to Module, Section, and pdf documents in this microbiology assessment are from the 04/30/15 original NDA submission.
- See NDA 208135, Information Requests (IR) dated 07/01/15, 10/26/15, and 12/20/15 for microbiology deficiencies conveyed to the applicant in support of this review.

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

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The subject drug product, Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT®, is a pre-sterilized ready-to-use topical anesthetic product for ocular use. The product has been manufactured and marketed by Alcon for over 45 years. It is a stable, non-preserved and single use product for pre-surgery use only.

- **Drug product composition –**

Component	Amount (% w/v)	Function/Purpose	Compendial Status
Tetracaine Hydrochloride	0.5[a] (b) (4)	Active	USP
Sodium Acetate (Trihydrate)	(b) (4)	(b) (4)	USP
Sodium Chloride			USP
Acetic Acid (b) (4)	Target pH 4.5	pH Adjustor	NF USP
Water for Injection	(b) (4)		USP

(b) (4)

(excerpt from 3.2.P.1, description-and-composition.pdf, p. 1 of 1, Table 3.2.P.1-1)

- **Description of container closure system –** The Alcon DROPTAINER® packaging system for the subject drug product consists of the following:

Component	Description
Bottle	Natural medium density polyethylene (b) (4) (b) (4) round bottle, 4 mL
Dispensing Plug	Natural low density polyethylene (LDPE) dispensing plug
Closure	White polypropylene (PP) closure

The bottle and plug are (b) (4) and the closure is sterilized by (b) (4) irradiation by (b) (4)

The primary container/closure (C/C) system is enclosed in a polyvinylidene chloride (PVC) blister with heat sealed Tyvek backing. This sterile, blister packed product is the STERI-UNIT® configuration.

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**

Primary packaging: Bottle, dispensing plug, cap
(07/15/15 Amendment, 3.2.P.2, Microbiological Attributes.pdf, link to report on p. 3 of 3, 11/13/15 Amendment, quality-information-amendment.pdf, p. 13 of 27)

Study/Report # and date: Microbiological Immersion Package Integrity Test Challenge - (b) (4) 3 mL Blended Bottles With LDPE Flat Tip Solution Plugs and (b) (4) Polypropylene Closures, Technical Report 032:38540:0598, 06/03/98

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Applicant's Response: See Section P.5 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

2.3.P.7 Container/Closure System

17. 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: See Section P.2.5 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

18. 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: See Section A.2 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

19. 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: See Section A.2 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommended/Adequate
Lisa S.G. Shelton 01/25/16

Secondary Review Comments and Concurrence: Concur with Reviewer's assessment of Recommended/Adequate
Bryan S. Riley, Ph.D.
Branch Chief (acting) OPQ/OPF/DMA/Branch II
1/25/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

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

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

Applicant's Response:

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Secondary Review Comments and Concurrence:

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

Labeling & Package Insert

For NDA only

1. Package Insert

APPEARS THIS WAY ON ORIGINAL

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Tetracaine Hydrochloride Ophthalmic Solution, 0.5%	Acceptable
Dosage form,	Yes	Acceptable

route of administration		
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Yes	Sterile ophthalmic solution containing 0.5% tetracaine hydrochloride (3)

Conclusion:
Revise to:
Sterile ophthalmic solution containing 0.5% tetracaine hydrochloride (b) (4)
(b) (4)

(b) "Full Prescribing Information" Section

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

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

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

Conclusion:
The applicant will be asked to revise the their statement in this section to remove the following: Sterile ophthalmic solution containing 0.5% tetracaine hydrochloride (b) (4)
(b) (4)

The current active tetracaine HCl name has no overage in terms of the label claim. The drug product meets the current USP monograph standards and maybe

inconsistent with its current general chapter <1121>. The USP assay limits are 90-110% same as the NDA proposes. Rather than recommending dropping the HCl from name, the applicant is asked to add the equivalency statement in label.
The 0.5% strength is calculated based on amount of tetracaine hydrochloride. For consistency with FDA's guidance on "Naming of Drug Products Containing Salt Drug Substances" and the USP Salt Policy, please propose an equivalent statement for label, e.g.: (b) (4)

Applicant's Response dated 1/15/2016: (Issue 4)

Response

An equivalency statement will be provided on the draft labeling.

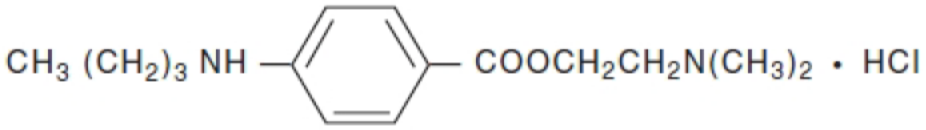
#11: Description (21CFR 201.57(c)(12))

(Attach proposed text)

11 DESCRIPTION

Tetracaine hydrochloride is an ester-linked local anesthetic.

Tetracaine hydrochloride is chemically designated as benzoic acid, 4-(butylamino)-,2-(dimethylamino) ethyl ester, monohydrochloride. Its chemical formula is $C_{15}H_{24}N_2O_2 \cdot HCl$ and it is represented by the chemical structure:



Tetracaine hydrochloride is a fine, white, crystalline, odorless powder and has a molecular weight of 300.82.

Tetracaine Hydrochloride Ophthalmic Solution 0.5% has a pH of 3.7 to 5.5.

Active ingredient: tetracaine hydrochloride 0.5% w/v (equivalent to 0.44% w/v tetracaine)

Inactive ingredients: sodium chloride, sodium acetate trihydrate, acetic acid (to adjust pH), Water for Injection, USP

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Yes	Acceptable
Dosage form and route of administration	Yes	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	No	Statement recommended to be added: tetracaine hydrochloride 0.5% w/v (equivalent to 0.44% w/v tetracaine). (b) (4) (b) (4)
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Yes	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological/ therapeutic class	Yes	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Yes	Acceptable

Conclusion:
Labeling recommendations are ongoing and have not been finalized.

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

16 HOW SUPPIED/STORAGE AND HANDLING

(b) (4)

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

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

17 PATIENT COUNSELING INFORMATION

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Yes	Manufacturer/distributor name listed at the end of PI, following Section #17. (b) (4)

Conclusion:

The NDC #0065-0741-12 provided in the drug label insert needs to revised. A search on the national drug code indicates a 2mL volume fill.

1) (b) (4)

Alcon has indicated the currently unapproved marketed drug is intended as the same with an overfill . The label declares a fill volume of 4mL.

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment:

Revise storage to: Store at 2°C to 25°C (36°F to 77°F)
Add equivalent statement: (b) (4) [redacted] (b) (4) [redacted].

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	It is not clear that "Steri-Unit" is the proposed established name.	Please comments in DMEPA review.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The 0.5% strength is calculated based on amount of tetracaine hydrochloride and not of the active base	Need to add equivalent statement to label.
Route of administration 21.CFR 201.100(b)(3))	Ophthalmic solution	
Net contents* (21 CFR 201.51(a))	The proposed contents on the label provided is 4 mL	
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information is provided.	
Lot number per 21 CFR 201.18	Information is provided.	
Expiration date per 21 CFR 201.17	Information is provided.	
"Rx only" statement per 21 CFR 201.100(b)(1)	Information is provided.	
Storage		
(not required)		
NDC number		
(per 21 CFR 201.2)		
(requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		

*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:
Please refer carton and container label review comments from Michelle Rutledge,

DMEPA.

(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))	It is not clear that "Steri-Unit" is the proposed established name.	Please comments in DMEPA review.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	The strength is provided.	
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Information is provided in PI and not on Blister Carton	Acceptable
Sterility Information (if applicable)	Please see comments below from labeling review	Acceptable
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		
Storage Conditions		
NDC number	The NDC #0065-0741-12 provided in the drug label insert needs to revised.	Please see comments
(per 21 CFR 201.2)		
(requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor	Provided	

"See package insert for dosage information" (21 CFR 201.55)		

Conclusion:

The NDC #0065-0741-12 provided in the drug label insert needs to revised. A search on the national drug code indicates a 2mL volume fill.

Alcon has indicated the currently unapproved marketed drug is intended as the same with an 100% overfill. The label declares a fill volume of 4mL.

Please refer carton and container label review comments from Michelle Rutledge, DMEPA.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

Labeling recommendations are ongoing and have not been finalized.

Milton J. Sloan, Ph.D.
Jan. 25, 2016

Secondary Review Comments and Concurrence:

I concur with the recommendations.

Balajee Shanmugam, Ph.D.
January 25, 2016

II. List of Deficiencies To Be Communicated

None