

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20583/S-028

Trade Name: LOTEMAX™

Generic Name: loteprednol etabonate ophthalmic suspension

Sponsor: Bausch & Lomb Pharmaceuticals, Inc.

Approval Date: 12/16/2013

Indication: LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation.

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**APPLICATION NUMBER:
NDA 20583/S-028**

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APPLICATION NUMBER:
NDA 20583/S-028

APPROVAL LETTER



NDA 20583/S-028, 20803/S-026

APPROVAL LETTER

Bausch & Lomb
Attention: Mary Harrell
Senior Manager, Regulatory Affairs
7 Giralda Farms Suite 1001
Madison, New Jersey 07940

Dear Ms. Harrell:

Please refer to your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA/Supplement	Drug Product	Date of Submission	Date of Receipt
20583/S-028	Lotemax® (loteprednol etabonate) Ophthalmic Suspension	August 23, 2013	August 23, 2013
20803/S-026	Alrex® (loteprednol etabonate) Ophthalmic Suspension	August 23, 2013	August 23, 2013

These “Prior Approval” supplemental new drug applications provide for:

- 1) removal of drug substance process related impurities from the drug product specification,
- 2) modifications to the analytical methodology for related substances to account for revised related substances correction factors,
- 3) tightening of the acceptance criteria for related substances in the drug product,
- 4) revision to the reporting parameters and acceptance criteria for particle size distribution.

We have completed our review of these supplemental new drug applications. These supplements are approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402-3815.

Sincerely,

{See appended electronic signature page}

Thomas F. Oliver, Ph.D.
Branch Chief, Branch VI
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

THOMAS F OLIVER
12/16/2013

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APPLICATION NUMBER:
NDA 20583/S-028

MEDICAL REVIEW(S)

Clinical Review of Bundled Prior Approval Supplements

Submission Date: August 23, 2013
Receipt Date: August 23, 2013
Review Date: December 12, 2013

NDA NUMBER	SUPPLEMENT NUMBER	PRODUCT NAME
020583	S-028	Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%
020803	S-026	Alrex (loteprednol etabonate ophthalmic suspension) 0.2%

Applicant: Bausch & Lomb
7 Giralda Farms, Suite 1001
Madison, NJ 07940

Applicant's Representative: Mary E. Harrell
Manager, Global Branded Rx Portfolio
& Regulatory Strategy Group
973-360-6462

Submitted:

Submitted are prior approval supplements containing Chemistry, Manufacturing and Controls (CMC) changes to the above referenced applications. The purpose of these supplements is to modify the drug product specifications and analytical procedures for related substances and particle size.

Specifically, the following changes are proposed in this supplement:

- Removal of drug substance process related impurities from the drug product specification.
- Modifications to the analytical methodology for related substances to account for revised related substances correction factors.
- Tightening of the acceptance criteria for related substances in the drug product.
- Revision to the reporting parameters and acceptance criteria for particle size distribution.

Reviewer's Comments:

For details of drug product specifications and analytical procedures for related substances and particle size for these two products, see the Chemistry review of these supplemental applications dated December 12, 2013.

Removal of the process related impurity specification is acceptable because there are other specifications in place which serve the same purpose. Modification to the analytical methodology is acceptable because it has been judged to be equivalent. Revision to the acceptance criteria is also considered equivalent.

Per the CMC review, the results provided fall within acceptance criteria and demonstrate that the proposed changes do not have an adverse effect on the reported final quality of the two drug products. We concur; the recalculated data provided in these supplements support the proposed changes

Recommendations:

These bundled supplements are recommended for approval.

William M. Boyd, M.D.
Clinical Team Leader

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/s/

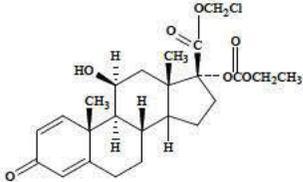
WILLIAM M BOYD
12/13/2013

WILEY A CHAMBERS
12/14/2013

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
NDA 20583/S-028

CHEMISTRY REVIEW(S)

Chemistry Review: # 1	1. Division: HFD-590	2. NDA Number: 20-583/S-028, Bundled with 20-803/S-026
3. Name and Address of Applicant: Bausch & Lomb 7 Giralda Farms Suite 1001 Madison, NJ 07940	4. Supplement(s): 20-583/S-028, Bundled with 20-803/S-026, PA Supplements Date(s): August 23, 2013 Stamp Date: August 23, 2013 Due Date: December 23, 2013	
5. Name of Drug: LOTEMAX® ALREX®	6. Nonproprietary name: (loteprednol etabonate ophthalmic suspension, 0.5%), and (loteprednol etabonate ophthalmic suspension, 0.2%)	
7. Supplements provide for: 1) removal of drug substance process related impurities from the drug product specification, 2) modifications to the analytical methodology for related substances to account for revised related substances correction factors, 3) tightening of the acceptance criteria for related substances in the drug product, 4) revision to the reporting parameters and acceptance criteria for particle size distribution: (Bundle)		8. Amendment(s): None
9. Pharmacological Category: anti-inflammatory	10. How Dispensed: R _x	11. Related Documents: NDA 20-803/S-026, August 23, 2013, Bundled supplement.
12. Dosage Form: Ophthalmic Suspension	13. Potency: Lotemax 0.5% Alex 0.2%	
14. Chemical Name and Structure: Loteprednol etabonate, C ₂₄ H ₃₁ ClO ₇ , MW 466.95, Androsta-1,4-diene-17-carboxylic acid, 17-[(ethoxycarbonyloxy)-11-hydroxy-3-oxo, chloromethyl ester, (11β, 17α) 		
15. Comments: These supplements provides for the modification of the drug product acceptance criteria and analytical procedures for related substances and particle size. These modifications are achieved through: <ul style="list-style-type: none">• Removal of drug substance process related impurities from the drug product specification.• Modifications of the analytical methodology for related substances to account for revised related substances correction factors.• Tightening of the acceptance criteria for related substances in the drug product specification sheet.• Revision to the reporting parameters and acceptance criteria for particle size distribution. <p>Minor modifications to the analytical methods are also proposed in these supplements.</p> <p>Stability data for 8 lots of Lotemax, (loteprednol etabonate ophthalmic suspension, 0.5%), at room temperature (25°C/40% RH) and for 6 lots of Alex (loteprednol etabonate ophthalmic suspension, 0.2%) at room temperature, using the proposed acceptance criteria for related compounds and particle size distribution are adequately provided.</p> <p>The two drug products in this bundled application are basically the same, loteprednol etabonate ophthalmic suspensions, the</p>		

only differences are the concentration of each, Lotemax 0.5% and Alex 0.2%, and the timing for the NDA approval of each product. For these reasons, the drug product specific, reanalyzed data, used to support the proposed modifications for each of the drug products (26 batches for related impurities and 149 batches for particulate size distribution for Lotemax, and 9 batches for related impurities and 72 batches for particle size distribution for Alex), support slightly different values for the proposed changes for impurities and particle size distribution for each product, yet, the proposed changes and trends for the two products are similar to each other.

The specific changes and values proposed for each of the products in this bundle are discussed and listed in the Chemistry Review Notes section of this review, below.

16. Conclusions and Recommendations: The rationale and recalculated data provided in this bundled supplement in support of the proposed changes are acceptable. For these reasons, from the point of view of CMC, these bundled supplements are recommended for **approval**.

17. Name:
Libaniel Rodriguez, Chemist

Signature:

Date:

18. Concurrence:
Hasmukh Patel, Branch Chief, Division VIII

Signature:

Date:

Chemistry Review Notes:**Removal of drug substance process related impurities from the drug product specification.**

The currently approved drug product specification includes both **specified process impurities** and specified degradation impurities. The **process related impurities** are also included in the current limit for total chromatographic impurities in the **drug product specification sheet**.

The process impurities proposed for removal from the drug product specification sheet are:



These process impurities are currently controlled in the **drug substance** specification sheet and will continue to be taken into account under the proposed **“Total Degradation Products”** acceptance criterion in the **Drug Product Specification Sheet**.

This action will harmonize the two drug products in this bundled application with the ICH standards, since under the **ICH Q6A Guidance**, drug substance process impurities that are controlled in the drug substance **do not need** to also be specifically delineated in the drug product specifications.

Evaluation: The effect of removal of the proposed process impurities from the drug product specification was evaluated by recalculating the “total process related impurities” at release and during stability for 26 batches of the drug product (Lotemax, 0.5%) studied. The results indicated that the total process related impurities were (b) (4) at release and no change was observed on the stability calculations. The results were well within acceptance criterion (Total Unknown (b) (4)). Similar results were observed for the recalculation using 9 batches of the bundled drug product (Alrex, 0.2%) in this application. **Based on these recalculated results, the proposed removal of the proposed process impurities listed above is acceptable.**

Revision of Related Substances Correction Factors:

The original validation of the identical HPLC procedures (b) (4) (for Lotemax, 0.5%) and (b) (4) (for Alrex, 0.2%) contained correction factors (Cf) that were erroneously assigned to each specified related substance, to account for the differences in response between the impurity and the active ingredient. These factors were set equal to the relative response factors (RRF) instead of the intended inverse of the RRF (1/RRF).

The existing data therefore was verified, reassessed and recalculated using the correct Cf value of 1/RRF. The results of this revision are shown below.

Current and Corrected Cf values for Lotemax, 0.5% Drug Product



Evaluation: The Cf values obtained through the use of the correct calculations are acceptable. The effect of the resulting changes in Cfs on the recalculations of overall results for related substances is shown and discussed in the next section.

Tightening of the acceptance criteria for related substances in the drug product specification sheet.

The effect of the correction factor changes on the overall results for related substances at release, before and after correction are shown in the tables below.

Results for Lotemax, 0.5% Drug Product.

Table 1.11.1-2 Comparison of release results for related substances assay C-1553 prior to and after correction factor adjustments

Component	Lot 143662		Lot 146491		Lot 149532	
	Prior to correction (b) (4)	After correction (b) (4)	Prior to correction (b) (4)	After correction (b) (4)	Prior to correction (b) (4)	After correction (b) (4)
Total Impurities		NA		NA		NA
Total Degradation Products		Beg: 0.31% End: 0.30%		Beg: 0.22% End: 0.27%		Beg: 0.26% End: 0.30%

NA = Not Applicable: The Total Impurities test result will be replaced by Total Degradation Product

Table 1.11.1-3 Comparison of stability ranges for related substances assay (b) (4) prior to and after correction factor adjustments

Parameter	Labeled Storage (25° ± 2°C/40 ± 5% RH through 24 months)		Accelerated Storage (30° ± 2°C/75 ± 5% RH through 24 months)	
	Prior to correction	After correction	Prior to correction	After correction (b) (4)
Total Unknown	< 0.05 to 0.26%	< 0.05 to 0.19%	< 0.05 to 0.18%	< 0.05 to 0.12%
Total Impurities	0.50 to 1.8%	NA	0.6 to 3.5%	NA
Total Degradation Products	NA	0.3 to 1.3%	NA	0.3 to 2.1%

NA = Not Applicable: The Total Impurities test result will be replaced by Total Degradation Product

Results for Alex, 0.2% drug product.

Table 1 Comparison of release results for related substances assay C-1554 prior to and after correction factor adjustments and removal of process impurities

Component	Lot 133291		Lot 130741		Lot 148191		Lot 150421	
	Prior to correction (b) (4)	After correction (b) (4)	Prior to correction (b) (4)	After correction (b) (4)	Prior to correction (b) (4)	After correction (b) (4)	Prior to correction (b) (4)	After correction (b) (4)
Total Degradation Products		Beg: 0.36% End: 0.37%		Beg: 0.32% End: 0.36%		Beg: 0.39% End: 0.39%		Beg: 0.39% End: 0.39%

Table 2 Comparison of stability ranges for related substances assay C-1554 prior to and after correction factor adjustments and removal of process impurities

Parameter	Labeled Storage (25° ± 2°C/40 ± 5% RH up to 24 months) ^a		Accelerated Storage (40° ± 2°C/20 ± 5% RH through 3 months)	
	Prior to correction	After correction	Prior to correction	After correction
(b) (4)				
Total Degradation Products	0.2 to 4.79%	0.12 to 2.76%	0.9 to 3.56%	0.68 to 2.79%

a Length of study depends on fill size (12 months for 1 mL, 15 months for 2.5 mL, 24 months for 5 and 10 mL fill sizes)

Evaluation: It is clear from the two sets of tables above that the use of the corrected Cf values bring about a substantial lowering of the release values for “Total Degradation Products” for both drug products, and in the case of the second set of tables (Alrex, 0.2%), the same is true after correction for Cf values and removal of process related substances on stability. These results are acceptable.

These recalculated values provide a more accurate view of the actual concentration of “Total Chromatographic Impurities” in these drug products, and leads to the following proposed revision/tightening to the related substances acceptance criteria in the drug product Specification sheets.

Lotemax 0.5% Drug Product.

(b) (4)				
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Alex, 0.2% Drug Product



(b) (4)

Evaluation: The tightening of the acceptance criteria proposed above is a result of the corrected calculations and the removal of process impurities from the drug product specification sheet; this represents an improvement on the control of “Total Chromatographic Impurities”, as well as on the final quality of the drug product. For these reasons, the proposed changes are acceptable.

Revision of Particle Size Distribution Reporting Parameters and Acceptance Criteria.

The current results for Particle Size Distribution provide for a limit on the allowed size of particles at the (b) (4) volumes, and at (b) (4). In order to harmonize with the current ICH Q6A Guidance, the applicant is proposing to report the particle size distribution by limiting the diameter size of the particles at the (b) (4) percentile volume, and at the (b) (4) and (b) (4) percentile volumes. This is done in order to comply with the ICH Q6A Guidance which recommends reporting at the middle, upper and/or lower portions of the Particle size Distribution.

The proposed changes are as follows:

Lotemax, 0.5% Drug Product



(b) (4)

Alex, 0.2% Drug Product

(b) (4)

Evaluation: It should be noticed from the tables above, that the proposed Dv values allow for a maximum particle diameter volume of (b) (4)

These proposed changes are acceptable.

Revision to analytical methods for related substances (HPLC methods (b) (4) for Lotemax and method (b) (4) for Alrex).

A minor method modification to the related substance procedure in the two identical methods above was made. An alternate resolution preparation was made as Option 2. In this alternate preparation two marker solutions are prepared with the (b) (4) included. This is implemented for the event in which the authentic standard resolution solution is not available.

The validation of this method is adequately provided and it includes the new Cf correction values reported in this submission. The validations results are as follows:

Lotemax, 0.5% Drug Product

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Evaluation: All the recalculated values reported for the validation of these two HPLC procedures are well within acceptance criteria. These results demonstrate that the methods are suitable for their intended purpose and that any minor changes and recalculation of parameters based on corrected Cf values do not have any adverse effect on the final results demonstrating the quality of the drug product.

Revision and validation of method (b) (4) for reporting Particle Size Distribution

The reporting parameters were discussed above, the validation of the method is reported below. The particle size distribution has been performed using a (b) (4) light diffraction particle size instrument equipped with the liquid dispersion small-volume recirculator. The current instrument is a **newer model** (b) (4) with similar operational principles.

This Particle Size Distribution Method is a USP (b) (4) method, which requires only a precision assessment for validation.

Lotemax, 0.5% Drug Product



Alex, 0.2% Drug Product



(b) (4)

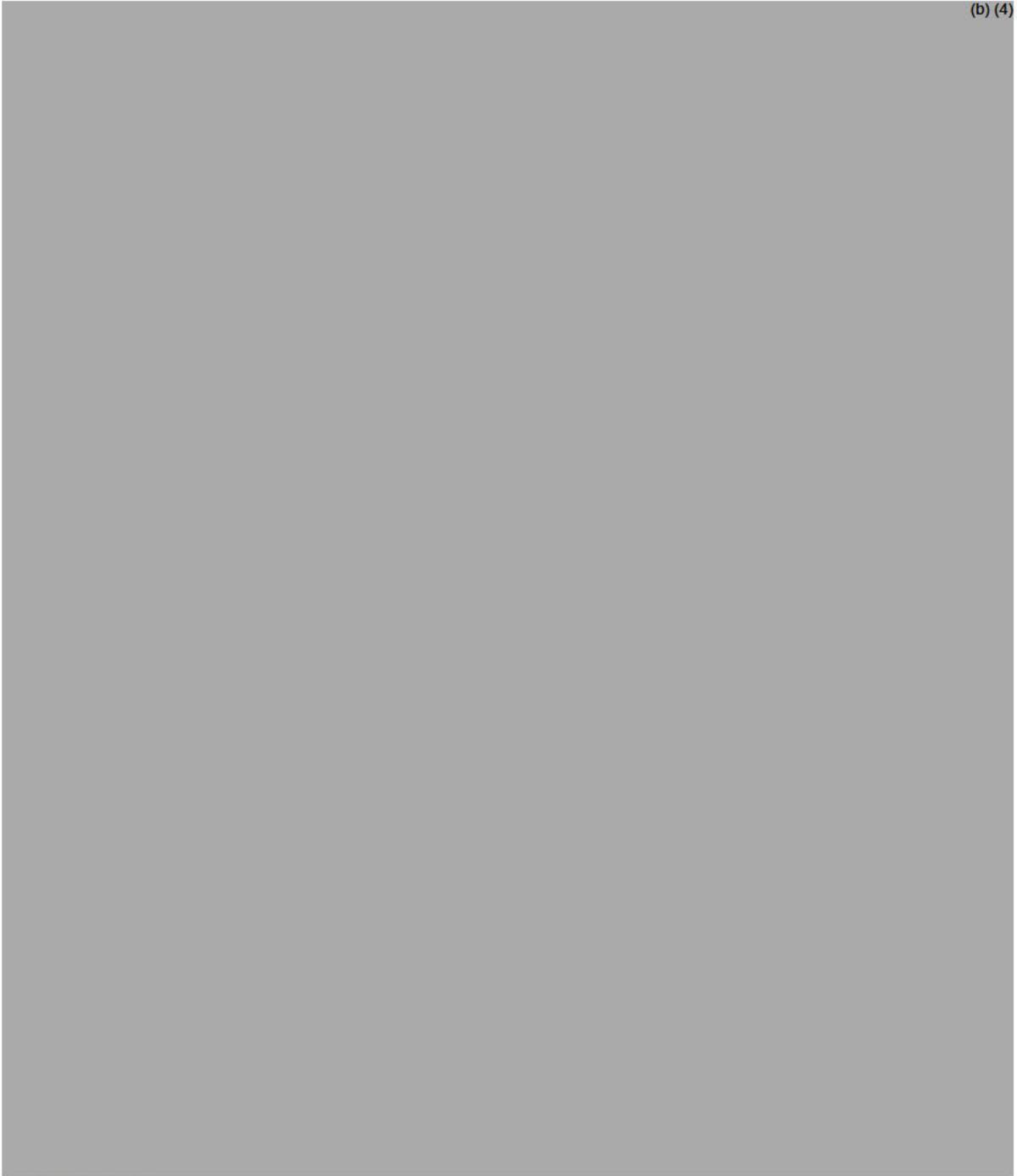
Evaluation: The results provided fall well within acceptance criteria for the two drug products involved in this application. The validated Particle Size Distribution method has therefore been demonstrated to be suitable for its intended purposes. For this reason, this method and proposed changes are acceptable.

Batch Analysis: Batch Analysis for three batches of commercial drug product including the Specification changes discussed through this review are shown below.

Lotemax, 0.5% Drug Product

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Alex, 0.2% Drug Product

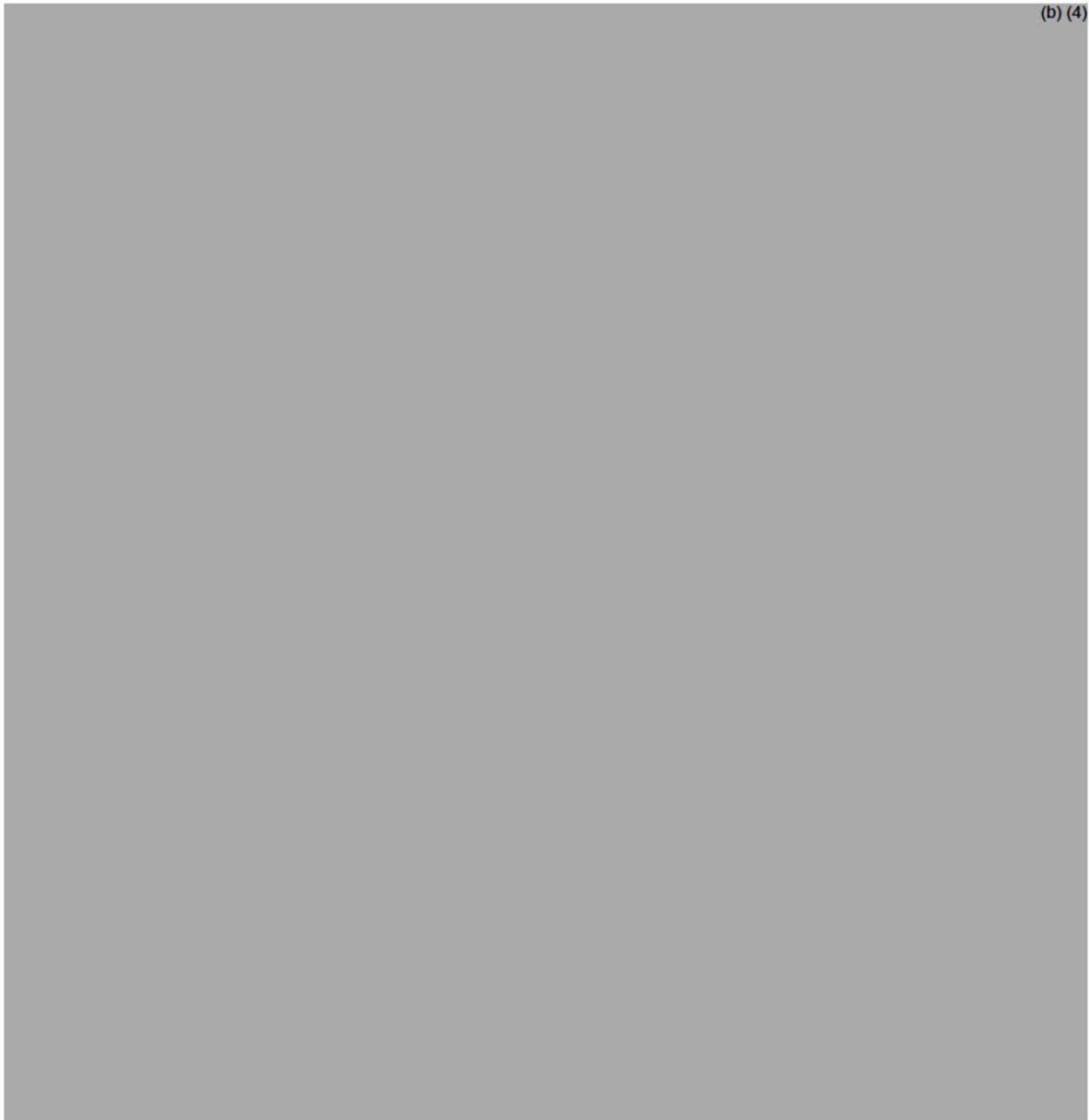


Evaluation: All the recalculated values for these batch analysis data fall well within acceptance criteria and demonstrate that the proposed changes have no adverse effect on the final quality of the drug products.

Final Accepted Specification Sheets:

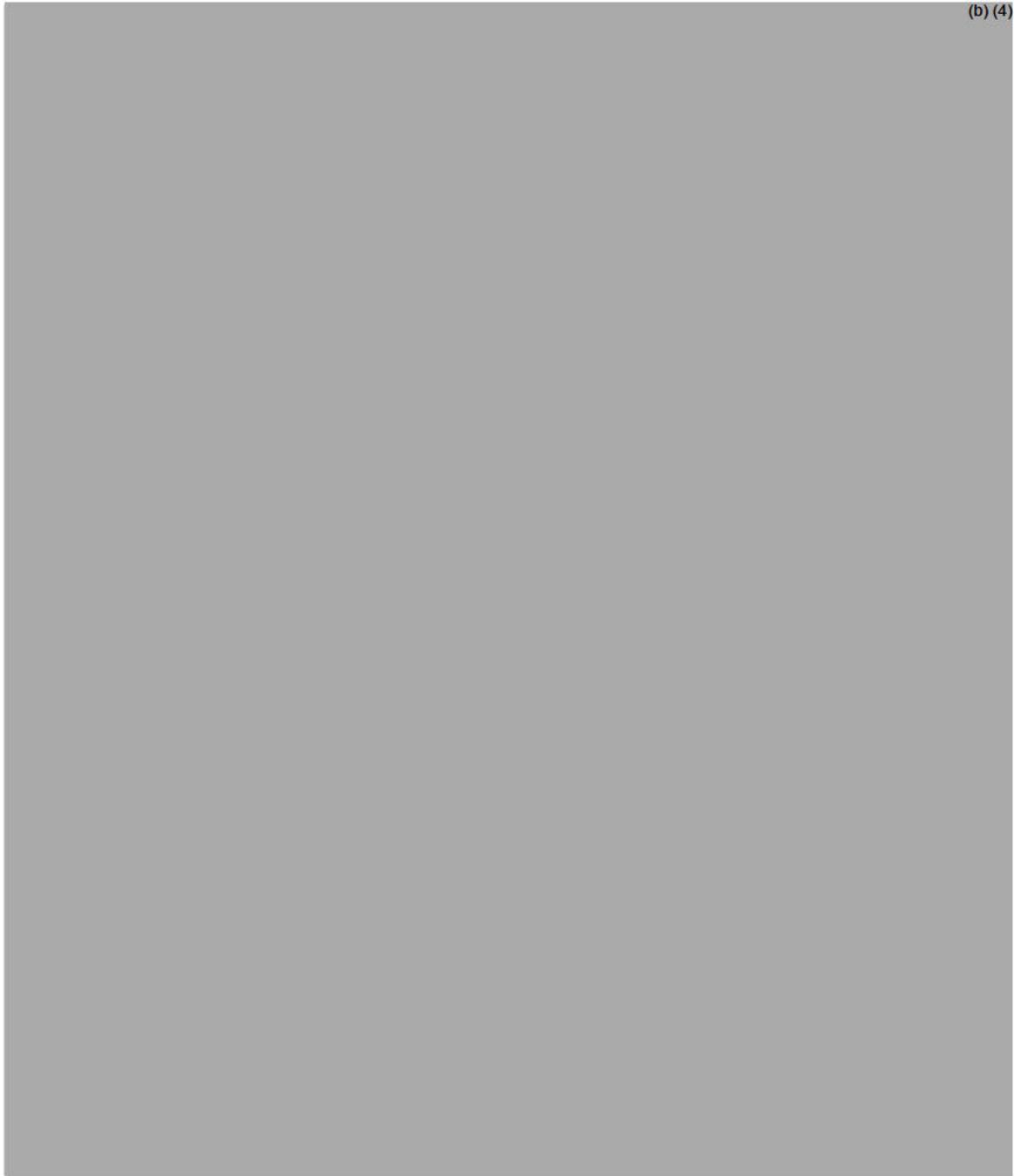
Based on the rationale and recalculated data provided, the following are the accepted Specification Sheets for the two drug products in this bundle:

Lotemac, 0.5% Drug Product



(b) (4)

Alex, 0.2% Drug Product



Evaluation: The rationale and recalculated data provided in support of the proposed, revised Specification sheets above are acceptable. Following the approval letter from this review, these will be the current Specification Sheets for the two drug products in this Bundle.

Stability Data: Recalculated stability data for several batches of the two drug products in this bundle were adequately provided. One set of representative data at room temperature (25°C/40% RH) for each of the drug products in this bundle is shown below.

Lotemax, 0.5% Drug Product

BAUSCH & LOMB INCORPORATED
8500 HIDDEN RIVER PARKWAY
TAMPA, FL 33637
(813) 975-7700

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LOT NUMBER: 057611
FILE NUMBER: 057611.RT0
STABILITY DATE: Oct 95, 2006
PRODUCT NAME: LOTEPREDNOL STABONATE OPHTH. SUSPENSION 0.5%
PRODUCT NUMBER: 222994
PRODUCT SIZE: 2.5 mL
CONTAINER: 7.5cc WHITE LDPE 3/8 BOTTLE (20-6064)
CLOSURE: 112:15mm WHITE LDPE CNTR. JCAP:15mm PINK P/P 3/S

TYPE OF MANUFACTURE: COMMERCIAL
MANUFACTURED AT: 8500 HIDDEN RIVER PARKWAY
DATE OF MANUFACTURE: 05/25/2006
EXPIRATION DATING: 12M 07/31/2007
COMMENTS: YEARLY - X057787
RAW MATERIAL MFG.: LOTEPRED. STAB.- PPG STPSY (XAZ1011) 051056433E
RAW MATERIAL MFG.:
RAW MATERIAL MFG.:
BATCH SIZE: 150 L

STORAGE CONDITION: 25+-2C/40+-5%RH UPRIGHT

Test Name	Test Specification	Test Method	0 MONTH	5 MONTHS	6 MONTHS	12 MONTHS	15 MONTHS				
DESCRIPTION		(b) (4)	PASS (05-27-06)	PASS (10-23-06)	PASS (12-04-06)	PASS (05-22-07)	PASS (07-30-07)				
CONTAINER DISTORTION & APPEARANCE			PASS (05-27-06)	PASS (10-23-06)	PASS (12-04-06)	PASS (05-22-07)	PASS (07-30-07)				
PH			5.1 5.0 (05-27-06)	4.5 4.5 (10-23-06)	4.4 4.4 (12-04-06)	4.2 4.2 (05-22-07)	4.2 4.1 (07-30-07)				
OSMOLALITY (mOsmol/kg) (OSM)			281 (05-27-06)	281 (10-23-06)	288 (12-04-06)	288 (05-23-07)	286 (07-30-07)				
BENZALKONIUM CHLORIDE (BAK)			100.1 99.5 (05-26-06)	100.8 101.2 (10-25-06)	96.7 96.6 (11-28-06)	101.9 101.6 (05-23-07)	97.8 97.7 (07-26-07)				
ROSTAYE DISODIUM DIHYDR. (RSD)			98.2 97.9 (05-26-06)	97.2 97.4 (10-21-06)	99.7 99.3 (11-27-06)	100.3 100.0 (05-22-07)	101.6 102.1 (07-26-07)				
LOTEPREDNOL STABONATE			131.7 132.4 (05-26-06)	99.9 99.0 (10-25-06)	131.4 132.0 (11-28-06)	101.6 101.2 (05-22-07)	103.3 104.3 (07-19-07)				
(b) (4)							(b) (4)				

3 months re-established T=0
NR: NOT REQUIRED PER PROTOCOL

Test Name	Test Specification	Test Method	0 MONTH	5 MONTHS	6 MONTHS	12 MONTHS	15 MONTHS				
TOTAL DEGRA. PRODUCTS (TDP)		(b) (4)	0.5 0.6 (05-26-06)	0.6 0.7 (10-25-06)	0.7 0.7 (11-28-06)	0.7 0.7 (05-22-07)	1.0 1.0 (07-19-07)				
RESUSPENSIBILITY		(b) (4)	PASS (05-27-06)	PASS (10-24-06)	PASS (12-04-06)	PASS (05-23-07)	PASS (07-11-07)				

5 months re-established T=0
NR: NOT REQUIRED PER PROTOCOL

STORAGE CONDITION: 25+2C/40+54RH UPRIGHT

Test Name	Test Specification	Test Method							
			3 MONTHS	6 MONTHS	9 MONTHS	12 MONTHS	15 MONTHS		
STERILITY (STP)	(b) (4)	PASS (35-30-06)	NR	NR	PASS (5-8-07)	PASS (8-1-07)			
ANTIMICROBIAL EFFECTIVENESS: TEST (APT)		PASS (10-19-06)	PASS (10-19-06)	NR	PASS (5-23-07)	PASS (7-19-07)			

5 months re-established T-3
NR: NOT REQUIRED PER PROTOCOL

Alex, 0.2% Drug Product

BMUSCH & LOMB INCORPORATED
8500 HIDDEN RIVER PARKWAY
TAMPA, FL 33637
(813) 975-7700

Nov 05, 2012 Page 1/3

LOT NUMBER: 277091
FILE NUMBER: 277091U.RC0
STABILITY DATE: Mar 07, 2008
PRODUCT NAME: LOTEPREDNOL ETABONATE 0.2% OPHTHALMIC SUSPENSION
PRODUCT NUMBER: Z235301
PRODUCT SIZE: 1 mL
CONTAINER: 4 mL WHITE LDPE BOSTON ROUND BOTTLE (20-6064)
CLOSURE: TIP:15mm LDPE WHITE; CAP:15mm PINK P/P L/S

TYPE OF MANUFACTURE: COMMERCIAL
MANUFACTURED AT: 8500 HIDDEN RIVER PARKWAY
DATE OF MANUFACTURE: 03/04/2008
EXPIRATION DATING: 12M 02/29/09
COMMENTS: FLTS - SCALE DOWN - IV-C353-K-06 - WHICH35301-02
RAW MATERIAL MFG.: KA21011 - 0704728049
RAW MATERIAL MFG.: S/A
RAW MATERIAL MFG.: S/A
BATCH SIZE: 150 LITERS

STORAGE CONDITION: 25+2C/40+54RH UPRIGHT

Test Name	Test Specification	Test Method							
			0 MONTH	3 MONTHS	6 MONTHS	9 MONTHS	12 MONTHS		
DESCRIPTION	(b) (4)	PASS (03-06-08)	PASS (06-18-08)	PASS (09-18-08)	PASS (12-20-08)	PASS (02-23-09)			
CONTAINER DISTORTION & APPEARANCE		PASS (03-06-08)	PASS (06-18-08)	PASS (09-18-08)	PASS (12-20-08)	PASS (02-23-09)			
PH		5.0 5.0 (03-06-08)	4.6 4.5 (06-18-08)	4.5 4.4 (09-18-08)	4.4 4.3 (12-20-08)	4.2 (02-24-09)			
OSMOLALITY (mOsmol/kg) (OSH)		286 (03-06-08)	294 (06-18-08)	296 (09-18-08)	298 (12-20-08)	302 (02-24-09)			
LOTEPREDNOL ETABONATE		101.7 99.4 (03-06-08)	100.6 98.5 (06-18-08)	104.9 101.2 (09-18-08)	104.4 106.2 (12-17-08)	102.2 (02-19-09)			
BENZALKONIUM CHLORIDE (BAK)		101.2 101.4 (03-06-08)	102.9 103.7 (06-10-08)	105.2 104.6 (09-17-08)	104.9 105.1 (12-13-08)	106.3 (02-19-09)			
EDCATE DISODIUM DIHYDR. (EDCA)		100.8 100.5 (03-06-08)	101.6 101.9 (06-10-08)	102.5 102.1 (09-13-08)	101.0 101.5 (12-16-08)	105.4 (02-19-09)			
(b) (4)					(b) (4)				

N/A: NOT APPLICABLE
NR: NOT REQUIRED PER PROTOCOL

Test Name	Test Specification	Test Method									
			0 MONTH	3 MONTHS	6 MONTHS	9 MONTHS	12 MONTHS				
			(b) (4)								
TOTAL DEGRA. PRODUCTS (TDP)			0.39 0.42 (03-06-08)	0.68 0.71 (06-03-08)	1.04 1.03 (09-13-08)	1.47 1.45 (12-17-08)	1.73 (02-19-09)				
			(b) (4)								
VISCOSITY			5.7 5.6 (03-11-08)	6.0 (06-12-08)	6.5 (09-13-08)	6.0 5.9 (12-19-08)	5.9 (02-24-09)				

N/A: NOT APPLICABLE
NR: NOT REQUIRED PER PROTOCOL

BUNDLED SUPPLEMENT DATA/STUDY RESULTS

Test Name	Test Specification	Test Method									
			0 MONTH	3 MONTHS	6 MONTHS	9 MONTHS	12 MONTHS				
RESUSPENSIBILITY			PASS (03-10-08)	PASS (06-12-08)	PASS (09-13-08)	PASS (12-19-08)	PASS (02-21-09)				
STERILITY (STR)			PASS (03-06-08)	NR	NR	PASS (12-23-08)	PASS (02-27-09)				
ANTIMICROBIAL EFFECTIVENESS TEST (AET)			PASS (03-12-08)	NR	NR	PASS (12-12-08)	PASS (03-04-09)				
WEIGHT LOSS/GAIN (WLG)			N/A	0.34 (06-04-08)	0.71 (09-12-08)	1.05 (12-12-08)	1.31 (02-19-09)				

N/A: NOT APPLICABLE
NR: NOT REQUIRED PER PROTOCOL

Evaluation: All the results provided fall well within acceptance criteria and demonstrate that the proposed changes do not have any adverse effect on the reported final quality of any of the two drug products in this bundle.

Conclusion: The rationale and recalculated data provided in this bundled supplement in support of the proposed changes are acceptable. For these reason, from the point of view of CMC, these bundled supplements are recommended for **approval**.

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/s/

LIBANIEL RODRIGUEZ
12/12/2013

THOMAS F OLIVER
12/12/2013

Initial Quality Assessment and Triage

ONDQA Branch VI

OND Division: HFD-590 (DTOP)

NDA: 20-583 (bundled with 20-803)

Supplement: S-028

DARRTS Document Number: SDN457

Applicant: Bausch & Lomb

Letter Date: 8-23-2013

Stamp Date: 8-23-2013

ONDQA Receipt Date: delivered to CMC lead on 8-26-2013

ONDQA CMC Lead triage date: 8-27-2013

Application Type: electronic

Proprietary Name: Lotemax® (loteprednol etabonate ophthalmic suspension, 0.5%)

Established Name: loteprednol etabonate ophthalmic suspension

Dosage Form: suspension

Route of Administration: ophthalmic

Submission Type: Prior-approval supplement (PAS)

Recommended submission type: PAS

Bundled with 20-803/S-025, Alrex® (loteprednol etabonate ophthalmic suspension, 0.2%)

This bundled electronic PAS proposes changes to the drug product specifications:

- Removal of drug substance process-related impurities from the drug product specification
- Modifications to the analytical methodology for related substances to account for revised correction factors
- Tightening of acceptance criteria for related substances in the drug product
- Revision to the reporting parameters and acceptance criteria for particle size distribution

Since the DS impurity control is unchanged, and the DP related substance specifications are unchanged, pharmacology might not have to review this. However, since the product is ophthalmologic, OND should be notified about these changes, and they should be asked whether they would want to manage this supplement.

This bundled electronic PAS proposes revisions to the drug product specifications, mainly involving impurities and related substances. This supplement concerns two NDA applications for ophthalmic suspensions:

- NDA 20-583, Lotemax® (loteprednol etabonate ophthalmic suspension, 0.5%)
- NDA 20-803, Alrex® (loteprednol etabonate ophthalmic suspension, 0.5%)

The following changes are proposed:

- Removal of drug substance process-related impurities from the drug product specification (these will continue to be controlled at the drug substance level)
- Modifications to the analytical methodology for related substances to account for revised related substance correction factors
- Tightening of acceptance criteria for related substances in the drug product
- Revision to the reporting parameters and acceptance criteria for particle size distribution

The changes proposed for the two application (20-583/S-028 and 20-803/S-025) are highly similar, but are not quantitatively identical, due to the difference in strength for the drug products. However, the justification and rationale behind the changes are the same, so these applications may be bundled.

(b) (4)

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/s/

DAVID B LEWIS

09/04/2013

IQA, PAS, see if clinical wants to manage

THOMAS F OLIVER

09/05/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20583/S-028

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 20583/S-028, 20803/S-026

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Bausch & Lomb
Attention: Mary Harrell
Senior Manager, Regulatory Affairs
7 Giralda Farms Suite 1001
Madison, New Jersey 07940

Dear Ms. Harrell:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA/ Supplement	Drug Product	Date of Submission	Date of Receipt
20583/S-028	Lotemax ® (loteprednol etabonate) Ophthalmic Suspension	August 23, 2013	August 23, 2013
20803/S-026	Alrex ® (loteprednol etabonate) Ophthalmic Suspension	August 23, 2013	August 23, 2013

These supplemental applications propose modifications to the drug product specifications and analytical procedures for related substances and particle size.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 22, 2013, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 23, 2013.

SUBMISSION REQUIREMENTS

Cite the application numbers listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NAVDEEP BHANDARI
09/04/2013