

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202872Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-872

Loteprednol Etabonate Ophthalmic Gel 0.5%

Bausch & Lomb Incorporated

Lin Qi
Branch V, ONDQA

For
Division of Transplant and Ophthalmology Products

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Chemistry Review Data Sheet

1. NDA 202-872
2. REVIEW #: 1
3. REVIEW DATE: 8/17/2012
4. REVIEWER: Lin Qi

5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

Amendment

Amendment

Amendment

Amendment

Document Date

11/29/2011

3/27/2012

6/15/2012

6/28/2012

7/27/2012

8/8/2012

7. NAME & ADDRESS OF APPLICANT:

Name: Bausch and Lomb Incorporated

Chemistry Review Data Sheet

Address: 7 Giralda Farms, Suite 1001
Madison, NJ 07940
Representative: Mary Harrell
Manager, Brand, Global Pharmaceutical Regulatory Affairs
Telephone: 973-360-6462
Email: mary_harrell@bausch.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: To be Determined
- b) Non-Proprietary Name (USAN): loteprednol etabonate ophthalmic gel, 0.5%
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Corticosteroid (Anti-inflammation)

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 0.5%

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

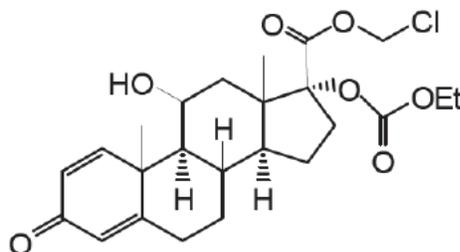
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

Chemical Names: Chloromethyl 17 α -[(ethoxycarbonyloxy)- 11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate



Molecular formula: C₂₄H₃₁ClO₇

Molecular weight: 466.96

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	5/31/2012 (L.Qi)	LOA 10/24/2011
	III			4	There is enough data in the application, therefore the DMF did not need to be reviewed.		
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

Chemistry Review Data Sheet

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102,654	Loteprednol Etabonate Ophthalmic Gel, 0.5%
NDA	20-583	Lotemax ® (loteprednol etabonate ophthalmic suspension, 0.5%)
NDA	20-803	Alrex® (loteprednol etabonate ophthalmic suspension, 0.2%)
NDA	200-738	Lotemax ® (loteprednol etabonate ophthalmic Ointment), 0.5%

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	3/20/2012	M. Stock
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Acceptable	8/17/2012	L. Qi
OPDRA			
EA			
Microbiology	Acceptable	8/9/2012	D. Miller

The Chemistry Review for NDA 202-872

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

An “Acceptable” site recommendation from the Office of Compliance has been made. Final labeling, proprietary name and dosage form name are pending team review.

From the CMC perspective, this NDA is recommended for *approval pending satisfactory resolution of all labeling and nomenclature issues*.

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

N/A

II. Summary of Chemistry Assessments

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

The drug substance, loteprednol etabonate, is a white to off-white powder. It is insoluble in water. Loteprednol etabonate (LE) is the same drug substance that is currently used in LOTEMAX (loteprednol etabonate ophthalmic ointment) 0.5% approved under NDA 200-738. The drug substance is manufactured (b)(4) DMF (b)(4) is referenced for drug substance information. The DMF is adequate. (b)(4) LE is (b)(4) The drug substance is tested by Bausch & Lomb Incorporated (B&L) in Tampa, Florida. During the review cycle, the drug substance impurity assignment for (b)(4) was corrected and batch analysis data were re-evaluated and corrected (S.4.4).

The drug product, loteprednol etabonate ophthalmic gel 0.5%, is a white to off white thixotropic gel for topical ophthalmic administration. The commercial drug product configurations are a nominal 5 g fill weight in a 10 mL LDPE bottle and a 0.5 g fill weight in a 4 mL LDPE bottle, both with (b)(4) tips, and pink polypropylene caps. The thixotropic gel converts to a fluid form (suspension) upon application of shear stress, and upon removal of shear, converts back to the gel form rapidly. Therefore, bottle inversion during patient use dispenses the drug product in a fluid form. The appropriate dosage form

Executive Summary Section

terminology to use for this drug product, whether gel or suspension, has not been finalized as of the date of this review.

The drug product, loteprednol etabonate ophthalmic gel 0.5%, will be manufactured at B&L's Tampa facility. The current formulation is manufactured (b) (4)

glycol, polycarbophil, sodium hydroxide, edetate disodium dihydrate, sodium chloride, tyloxapol, benzalkonium chloride, sodium hydroxide, and water for injection. All ingredients to be used are USP/NF grade and have been used in other marketed ophthalmic products at higher concentrations. Each of these excipients is tested to ensure conformance to the current requirements of the USP monograph. A (b) (4) overage of the drug substance, loteprednol etabonate, is added (b) (4). A (b) (4) overage of the antimicrobial preservative (benzalkonium chloride) is used (b) (4).

Tests included in the drug product specification are Description, Container Description, Particulate Matter, Identification (HPLC and UV), Loteprednol Etabonate Assay, Container Content Uniformity, Related Substances, Benzalkonium Chloride Assay, Particle Size Distribution, pH, Viscosity, Osmolality, Sterility, Antimicrobial Effectiveness (for stability only), Weight Loss/Gain (for stability only), Endotoxin (at release only), Fill Weight (at release only). Final acceptance criteria were established for all specification tests except for viscosity, where a tentative acceptance criterion was established (P5.6). The viscosity specification is subject to change, if appropriate, when additional release and stability data from full-scale process validation batches are obtained. The change will be reported via the post-marketing supplement process.

Container components are (b) (4). A leachable arising (b) (4) is controlled through drug product specification (P5.1 and P5.6). In-use dosing uniformity of the drug product was demonstrated by supporting data (P.2.2.3).

The proposed expiry period for the drug product is 24 months (for the 5 g fill size) and 12 months (for the 0.5 g fill size) at a storage temperature of 15 - 25°C (59 - 77°F) (b) (4). Stability data provided up to 24 months at 25°C/40%RH and 30°C/75% RH and 6 months at 40°C/20%RH, and regression analysis support the proposed expiration periods proposed for the 5 and 0.5 g fill sizes. The annual drug product stability samples will be stored in a horizontal orientation for the worst case scenario (P.8.2).

Executive Summary Section

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

The drug product, loteprednol etabonate ophthalmic gel 0.5%, is indicated for the treatment of inflammation and pain following ocular surgery. The proposed administration instruction is:

(b) (4)

Apply one or two drops of TRADENAME™ into the conjunctival sac of the affected eye(s) four times daily after surgery and continuing throughout the first 2 weeks of the post-operative period.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The product quality microbiological review dated August 8, 2012 recommended approval from a quality microbiology standpoint. An "Acceptable" site recommendation from the Office of Compliance has been made on March 20, 2012. The labeling is pending team review and the proprietary name and dosage form of the drug product are still under discussion.

Therefore, this NDA is recommended for *approval pending resolution of all labeling and nomenclature issues.*

III. Administrative**A. Reviewer's Signature**

See Signature in DARRTS.

B. Endorsement Block

ChemistName/Date: Lin Qi/8/17/2012
BranchChiefName/Date: Rapti Madurawe/8/17/2012
ProjectManagerName/Date: Althea Cuff/8/17/2012

C. CC Block

See cc list in DARRTS.

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/s/

LIN QI
08/17/2012

RAPTI D MADURawe
08/17/2012

Initial Quality Assessment Branch V
Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products
NDA: 202-872

Applicant: Bausch and Lomb

Stamp Date : 29 November, 2011

Proposed Trademark: (b) (4)

Established Name: Loteprednol etabonate ophthalmic gel 0.5%

Dosage Form: Ophthalmic gel

Route of Administration: Topical

Strength: 0.5%

Indication: a. Treatment of inflammation & pain following ocular surgery

(b) (4)

Reviewer : Lin Qi

CMC Lead : Bala Shanmugam

	YES	NO
Acceptable for filing:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter:	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues

Summary

Loteprednol etabonate ophthalmic gel 0.5% has been submitted, as noted above, (b) (4)

(b) (4)
The NDA is filed as a 505 (b) (1). The submission, including methods validation is all electronic and located in the EDR. The drug product is formulated as a sterile ophthalmic gel for topical administration and the proposed commercial package is 5 g in 10 mL LDPE bottle. Additionally, a physician sample size of 0.5 g fill weight in 4 mL LDPE bottle is also being proposed. (b) (4)

(b) (4)
Loteprednol etabonate API has been previously approved and marketed as an ophthalmic suspension (0.2%, and 0.5%) and as an ointment (0.5%). The company is requesting a shelf-life of 24-months for the 5 g fill size and 12-months for the 0.5 fill size (sample) when stored at 15-25°C.

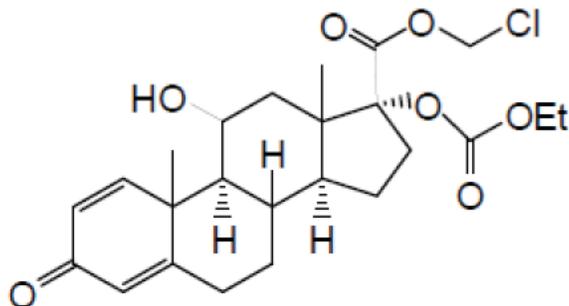
OSE has completed evaluation of the proposed proprietary name and concluded that it is unacceptable. All manufacturing and testing facilities have been entered in EES.

* OSE found the proposed name unacceptable

The IND related to this submission is IND 102654. Please note that a pre-IND, EOP2 and a pre-NDA meeting was held. The minutes of the Pre-NDA meeting is attached to this IQA for quick reference to the reviewer.

This NDA will be reviewed on a Standard time line. The PDUFA goal date is September 29, 2012.

Drug Substance



All drug substance information related to manufacturing (b)(4) and controls is referenced to DMF (b)(4) (see table for status of this DMF at the time of this IQA). A letter of authorization from the DMF holder has been provided.

Drug Substance	DMF #	LOA provided (Yes/No)	Status	Comments
Loteprednol etabonate	(b)(4)	Y	The last review is by Anamitro Banerjee, dated February 17, 2011.	There is one Quality submission on stability and an Annual Report which requires to be reviewed.

- Loteprednol etabonate synthesized from prednisolone is manufactured by (b)(4)
- The (b)(4) drug substance is sterilized via (b)(4). The sterility part of the DMF may have to be evaluated by the Product Quality Microbiology Reviewer.
- The specification for the sterile drug substance includes a test for (b)(4). *It needs to be clarified why the sterilization procedure (b)(4) is part of the specification. The sterilization protocol should specify the (b)(4) required for sterilization and hence the inclusion of this process as a test requires to be clarified. There are some minor differences in the acceptance criteria for some of the quality attributes (such as assay and particle size) between the non-sterile and sterile drug substance specification. This should be verified to be adequately justified.*

- The NDA does not seem to provide details (dimensions, supplier etc) on the (b) (4) used for packaging the drug substance. Either a certificate of analysis for the (b) (4) or a statement that it conforms to 21 CFR 175.320 and/or other CFR requirements should be provided.
- Stability data of the sterile drug substance is provided in the NDA submission and includes data from initial lots and those lots manufactured recently. The proposed retest date is (b) (4) when stored at $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$.

Drug Product

The product is formulated as a sterile ophthalmic gel.

- The drug product is manufactured by Bausch and Lomb, Inc., FL.
- All excipients used in the formulation are compendial
- The function of the Polycarbophil (b) (4) excipient is to (b) (4)
- Benzalkonium chloride is used as a preservative
- A (b) (4) overage of loteprednol etabonate and (b) (4) overage of benzalkonium chloride are being added to offset losses. *The reviewer should evaluate the justification provided by the company for the proposed overages.*
- The drug product composition is attached to this review
- Manufacturing process involves (b) (4)
- Data for the exhibit batches (b) (4) have been provided.
- As mentioned above, a fill size of 10 g in 15 mL bottle, (Lot number 427611; Table 3.2.P.8.1-1, summary of stability lots), is indicated to have been used in clinical trial. However, Table 3.2.P.5.4-1 (batch analysis) indicates Lot number 427611 of fill weight 5 g. Additionally, the Clinical Section 16.1.6 indicates the use of lot number 247231 in clinical studies but it seems that quality data for this batch has not been submitted. *The reviewer should clarify both these issues.*
- The DP specification is attached to serve as a quick reference for the reviewer. The company has proposed separate release and regulatory specification with differences in acceptance criteria for assay, related substances (b) (4) total related substances (b) (4) for stability specification compared to (b) (4) in release specification) and BAK (80-120% in stability as compared to 90-110% for release specification). *These acceptance criteria proposed for the aforementioned quality attributes and the one proposed for*

viscosity should be evaluated and (b) (4) if needed as based on batch and stability data. Please note that the company has proposed a test for container description. The reviewer should determine the value of this test in the specification. The specification does not provide a test for residual solvents. The company claims that (b) (4). The company in addition to mentioning that the drug product meets the requirements of ICH Q3C, option 1, should provide a statement that the drug product complies with USP <467>.

- Particle size distribution, sterility and viscosity are the key quality attributes of this drug product formulation.
- The trend in quality attributes on stability, specifically (b) (4) should be evaluated in considering the proposed shelf-life of 24-month and how it affects, if any the shelf-life attributes of the drug product.
- A leachable peak identified as (b) (4) is reported to remain at a level of (b) (4). A toxicology consult on this leachable should be pursued. The reviewer should determine if this leachable should be added to the DP specification. Additionally, the company mentions that it is currently evaluating (b) (4) to eliminate this leachable. An update on this should be requested. If warranted, a post-approval commitment maybe pursued.
- The container closures are sterilized using (b) (4).
- The label for (b) (4) fill mentions “Sample-Not for sale”. It should be determined with Clinical/DMEPA if this is adequate or should the label specifically state “Physician sample”.

Early action needed:

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

Comments for 74-day letter

None at this time.

Comments and Recommendation:

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

Balajee Shanmugam
CMC Lead

See DARRTS
Date

Rapti Madurawe, Ph.D.
Branch Chief

See DARRTS
Date

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/s/

BALAJEE SHANMUGAM
01/24/2012
N202872IQA

RAPTI D MADURawe
01/24/2012

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

NDA Number: 202-872

Supplement Number and Type:

Established/Proper Name:

Lotepredonal etabonate
ophthalmic gel, 0.5%

Applicant: Bausch and
Lomb

Letter Date: 29-Nov-2011

Stamp Date: 29-Nov-2011

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

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		There were three meetings with the Agency over the course of development of the drug product. A PIND and an EOP2 meeting were held under IND 102654 and more recently a Pre-NDA meeting. The Pre-NDA meeting minutes will be attached to the IQA.

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?		✓	The facilities have been identified with contact information in the appropriate drug substance and drug product sections.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

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

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>The Drug substance is referenced to DMF (b) (4) and a LOA has been provided.</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	✓		

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

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	✓		Yes, statement provided in the cover letter.

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

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

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

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			The drug substance is referenced to DMF (b) (4) LOA has been provided in the NDA.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Referenced to DMF
14.	Does the section contain information regarding the characterization of the DS?			Referenced to DMF
15.	Does the section contain controls for the DS?			Referenced to DMF
16.	Has stability data and analysis been provided for the drug substance?	✓		Stability data for the sterile drug substance is provided in the submission.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		✓	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		✓	

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

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

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

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

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

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

DMF # (b)(4)	TYPE	HOLDER	ITEM REFERENCED (b)(4)	LOA DATE	COMMENTS
	II			10-24-11	
	III			05-11-11	
	III			05-11-11	
	III			10-26-11	
	III			05-23-11	
	III			05-25-11	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	✓		
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		✓	

{See appended electronic signature page}

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

Date

{See appended electronic signature page}

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

Date

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