CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208219Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 208219 (loteprednol etabonate ophthalmic gel, 0.38%)

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

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

Date: Feb-22-2019

Re: Approval recommendation from product quality perspective

Drug substance, drug product, biopharmaceutics, manufacturing process and quality micro reviewers have recommended approval of NDA 208219 as documented in Review #1.

As documented in this Addendum, the drug product manufacturing facility, Bausch & Lomb (FEI:1000113778) is classified as NAI based on the recent inspection ending Jan 30, 2019. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on Feb 22, 2019. Therefore, NDA 208219 is recommended for APPROVAL from the product Quality perspective.

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

Chunchun Zhang, Ph.D.
ATL for 208219

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QUALITY ASSESSMENT

Recommendation: Complete Response

NDA 208219
Review # 1
Jan 24, 2019

Drug Name/Dosage Form	***loteprednol etabonate ophthalmic gel***
Strength	*0.38%*
Route of Administration	*Topical ophthalmic*
Rx/OTC Dispensed	*Rx*
Applicant	*Bausch & Lomb*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*4/25/2018*
Amendment	*6/13/2018*
Amendment	*7/6/2018*
Amendment	*7/23/2018*
Amendment	*10/25/2018*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Kabir Mohd Shahjahan	Su (Suong) Tran
Drug Product	David Claffey	Chunchun Zhang
Microbiology	David Bateman	Julie Nemecek
Biopharmaceutics	Kaushalkumar Dave	Jing Li
Process	Nancy Waites	Dan Obrzut
Facility	Nancy Waites	Dan Obrzut
Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	David Claffey	Chunchun Zhang

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	12/10/2018	LoA: 8/25/2017 Kabir Mohd Shahjahan
	Type III			NA		LoA: 8/30/2017
	Type III			NA		LoA: 11/14/2017
	Type III			NA		LoA: 8/17/2017
	Type III			NA		LoA: 1/21/2013
	Type III			NA		LoA: 9/8/2017
	Type III			NA		LoA: 1/21/2013

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102654	
NDA	202872	Approved loteprednol etabonate ophthalmic gel, 0.5%

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		10/9/2018	Andrew J. McDougal
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality micro, manufacturing process, and biopharmaceutics aspects.

The compliance status of the drug product manufacturing facility, Bausch & Lomb (FEI 1000113778), was found withhold based on the most inspection performed ending Aug 10, 2018. Therefore, OPF has issued an overall recommendation of "Withhold" on 1/7/2019. In agreement with the above recommendation, NDA 208219 is recommended for Complete Response from Product Quality perspective.

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

The following CR statement about the unacceptable manufacturing facility (Bausch & Lomb) should be included in the CR letter:

During a recent inspection of the Bausch & Lomb (FEI 1000113778) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	For the treatment of post-operative inflammation and pain following ocular surgery.
Duration of Treatment	One drop topically in the eye(s) three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period. See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance, loteprednol etabonate, is a white to off-white crystalline powder. It is manufactured by (b) (4). The drug substance referenced in DMF (b) (4) was found adequate by Kabir Mohd Shahjahan on 12/10/2018.

ii. Drug Product Quality Summary

Loteprednol etabonate ophthalmic gel, 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery. The drug product is 5 g-fill gel in 10 mL (b) (4) white LDPE round bottle, fitted with (b) (4) white (b) (4) controlled drop tip and capped with a (b) (4) pink, polypropylene, (b) (4) closure. The physician sample is proposed as 0.5 g fill in a 4 mL container closure system of the same composition.

The applicant has an approved marketed product with 0.5% strength which is similar to the proposed product. All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. BAC is the preservative in the formulation. The drug product specification includes tests for appearance, identity, assay, impurities (specified, unspecified and total), BAC assay, pH, osmolality, viscosity, weight loss, content uniformity, sterility, particulate matter, antimicrobial effectiveness, particle size distribution, and minimum fill weight. The proposed impurities limits are found acceptable by the pharm/tox reviewer Dr. Andrew J. McDougal on 10/9/2018. The applicant aimed to increase the bioavailability of the drug substance in the proposed product by reducing the particle size from a median of (b) (4) um in the marketed product to (b) (4) nm. The applicant has performed extractable and leachable studies, no reportable extractable or leachable was detected. The container closure system is the same as the currently marketed product 0.5% strength. All analytical methods are described in reasonable detail and have been adequately validated.

The applicant has submitted 3 batches at the (b) (4) kg scale and 2 batches at the (b) (4) kg commercial scale using the commercial process and packaging for both the commercial (5g) and physician sample (0.5g) containers. Data through 15 months was available for the 0.5 g size and through 24 months for the commercial 5 g size at 25°C/40%RH. No accelerated study was performed. All the quality attributes remain within the proposed specifications. Therefore, the expiration date of 24 months for the commercial (5g) and 12 months for physician sample is granted when stored at 15 °C- 25 °C.

The storage statement is "Store at 15°C to 25 °C (59ºF-77ºF)." and will be finalized at the OND's labeling meeting.

The proposed drug product manufacturing process consists of (b) (4)

[redacted] (b) (4) During the NDA review several information requests regarding to validation plan and extractable/leachable [redacted] (b) (4) were conveyed to and addressed by the applicant. The overall information regarding the manufacturing process provided in the NDA submission and subsequent amendments was found acceptable. The drug product is [redacted] (b) (4) into either 4 mL or 10 mL bottles. It is found acceptable from quality micro perspective.

Biopharmaceutics reviewer Dr. Dave has found in-vitro and/or in-vivo bridging studies are not needed. The applicant proposed to develop an appropriate IVRT method post-approval which is found acceptable.

OPF has issued a withhold recommendation for the drug product manufacturing site Bausch & Lomb at Tampa, FL (FEI: 1000113778) from the outcome of the recent inspection. All the other facilities are acceptable based on the profile. Therefore, the overall recommendation of "withhold" was entered for the NDA into Panorama by OPF on 1/7/2019.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site	H	Sterilization has been validated.	L	Post-approval stability protocol will test sterility.
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	L	This is a topical product and therefore does not require testing for endotoxin.	L	No endotoxin testing required.

Assay (API), stability	Formulation Container closure[1] Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Assay (preservative)	Formulation Container closure[1] Process parameters Scale/equipment	L	Preservative BAC is added in the formulation.	L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	M	A white to off-white ophthalmic gel. A fill volume of 5g in a 10 mL LDPE bottle for commercial and 0.5 g in a 4 mL LDPE bottle for physician sample.	L	
pH	Formulation Container closure[1] Process parameters Scale/equipment	L	Buffered formulation; No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particle size	Formulation Container closure[1] Process parameters Scale/equipment	M	Particle size distribution was included in the drug product specification.	L	

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

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

On behalf of the OPQ team
Chunchun Zhang, Ph.D. ATL for NDA 208219

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MICROBIOLOGY

Product Background:

NDA: 208219

Drug Product Name / Strength: Loteprednol etabonate ophthalmic gel 0.38%, multi-dose

Route of Administration: Ophthalmic

Applicant Name: Bausch & Lomb Incorporated

Manufacturing Site:
Bausch & Lomb, Inc.
8500 Hidden River Parkway
Tampa, FL 33637

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

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

Justification (ANDA only): N/A

Review Summary: The drug product is (b) (4) into either 4 mL or 10 mL bottles.

List Submissions Being Reviewed: April 25, 2018, October 25, 2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This drug product application contains a slightly lower concentration of a drug product previously approved in a new drug application.

Concise Description Outstanding Issues Remaining: None.

Supporting Documents

NDA 202872 – N202872N000R1.doc, dated August 6, 2012. For review of information related to the (b) (4) drug substance. (Accepted)

S Drug Substance

(1.4.4 Cross Reference to previously submitted information)

The drug product is [redacted] (b) (4). The applicant references the previously approved NDA 202872 and IND 102654 for all manufacturing, packaging, specifications and stability related to the (b) (4) drug substance, as agreed upon by the Agency in a Pre-NDA meeting held on January 30, 2018 (cross-reference.pdf, pages 1, 16). NDA 202872 is similar to this application with a final drug product concentration of 0.5% rather than the final drug product concentration of 0.38% filled for this NDA.

Adequate

Reviewer's Assessment: The manufacturing and drug substance details were reviewed and accepted in Microbiology review N202872N000R1.doc, dated August 6, 2012. See this review for further information.

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** A sterile white to off-white gel for topical ophthalmic administration.

- **Drug product composition:**

Ingredient	Content mg/g fill	Content % (w/w)
Loteprednol etabonate, (b) (4)	(b) (4)	0.38%
Glycerin, USP		(b) (4)
Propylene glycol, USP		
Sodium chloride, USP		
Benzalkonium chloride, NF		0.003%
Polycarbophil, USP		(b) (4)
Hypromellose (b) (4), USP		
Sodium hydroxide, NF		
Poloxamer 407, NF		
Edetate disodium dehydrate, USP		
Boric acid, NF		
Water for injection, USP		

- **Description of container closure system:**

Component	Description	Manufacturer
Bottles	4 mL and 10 mL white (b) (4) round bottles.	(b) (4)
Tip	15 mm white (b) (4) controlled drop tip	
Cap	15 mm Polypropylene, pink (b) (4) with (b) (4).	

Adequate

Reviewer's Assessment:

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

(b) (4)

Adequate

Reviewer's Assessment:

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(b) (4)

P.5 Control of Drug Product

P. 5.1 Specification

(3.2.P.5.1 Specifications)

The product release specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP<71>	Must be sterile

Adequate

Reviewer's Assessment:
The applicant conducts USP <71> sterility testing. Since the drug product is an ophthalmic, endotoxin testing is not required and not performed.

P.5.2 Analytical Procedures

Not Applicable
Reviewer's Assessment: See section P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

Sterility

(3.2.P.5.3 Validation of analytical procedures Sterility USP 71)
Test Method: Equivalent to USP<71>

Bacteriostasis/fungistasis testing was performed. The subject drug product was tested using *Pseudomonas aeruginosa* ATCC 9027, *Staphylococcus aureus* ATCC 6538, and *Clostridium sporogenes* ATCC 11437 using fluid thioglycolate medium (FTM). *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC 10231, and *Aspergillus brasiliensis* ATCC 16404 were tested using tryptic soy broth (TSB). Ten units of the 2.5 mL sample are transferred into 100 mL of TSB and ten units of the 2.5 mL samples are transferred into 100 mL of FTM and then each are inoculated with less than 100 colonies of challenge microorganism. The TSB bottles are incubated at 20-25 °C and the FTM bottles are incubated at 30-35 °C for five days.

The subject drug product did not inhibit recovery of the test organisms and the applicant notes that the growth was comparable to positive controls.

Adequate

Reviewer's Assessment:
The applicant provided an acceptable summary of the sterility test validation.

P.7 Container Closure

Not Applicable

Reviewer's Assessment: See section P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 Stability summary and conclusion)

The applicant proposes an expiry of 12 months for the 0.5 g in 4 mL bottle configuration based on 15 months of data and an expiry of 24 months for the 5 g in 10 mL bottles based on 24 months of data.

Adequate

Reviewer's Assessment:
The applicant's proposed expiry is acceptable based on provided microbial data.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(3.2.P.8.2 Post approval stability protocol and stability commitment)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Antimicrobial effectiveness	USP<51>	Meets USP
Sterility	USP<71>	Sterile

The testing schedule for the 0.5 g 4 mL configuration in the post-approval protocol is as follows:

Stability storage conditions: 25 °C at 40% RH

Test	Time (Months)							
	0	3	6	9	12	15*	24	36
Bacterial Endotoxins	X				X	X		
Sterility	X				X	X		

The testing schedule for the 5 g in 10 mL configuration in the post-approval protocol is as follows:

Stability storage conditions: 25 °C at 40% RH

Test	Time (Months)							
	0	3	6	9	12	15	24	36*
Bacterial Endotoxins	X				X		X	X
Sterility	X				X		X	X

* The Applicant has indicated that these time points are optional.

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program for each fill size.

Adequate

Reviewer's Assessment:
The applicant provided an acceptable stability program for microbial testing.

P.8.3 Stability Data

(3.2.P.8.3 Stability data)

The applicant provided results from sterility and antimicrobial effectiveness testing up to 24 months for the 5g in 10 mL bottle configuration and up to 15 months for the 0.5g in 4 mL bottle configuration for (b) (4) kg and (b) (4) kg lots.

Adequate

Reviewer's Assessment:
The applicant provided acceptable microbiology stability data.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Not Applicable

Reviewer's Assessment: N/A

A.2.1 Materials of Biological Origin

Not Applicable

Reviewer's Assessment: N/A

A.2.2 Testing at Appropriate Stages of Production

Not Applicable

Reviewer's Assessment: N/A

A.2.3. Viral Testing of Unprocessed Bulk

Not Applicable

Reviewer's Assessment: N/A

A. 2.4 Viral Clearance Studies

Not Applicable

Reviewer's Assessment: N/A

R Regional Information

Executed Batch Records

The batch records confirm that validated (b) (4) were used for the manufacture of the exhibit batches.

Adequate

Reviewer's Assessment:
The applicant provided detailed batch records for batches 238161 and 238162, which used the described manufacturing processes.

Comparability Protocols
None Provided

Not Applicable

Reviewer's Assessment: None provided.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert
(1.14.1.3 Draft labeling text)

(b) (4)

The package insert states that the dropper tip should not touch any surface, as this may contaminate the gel.

The applicant provided in use studies to demonstrate the microbial stability of the product after (b) (4) 28 days. Two lots had 3 drops daily dispensed for 5 days per week for up to 28 days, then sterility and antimicrobial effectiveness testing was conducted. Both lots passed (stability-summary.pdf, page 23-27).

Adequate

Reviewer's Assessment:
The applicant provided acceptable instructions to maintain drug product microbiological stability.

Post-Approval Commitments:

Not Applicable

Reviewer's Assessment: N/A

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:

David Bateman, Ph.D.
December 5, 2018
Secondary Reviewer Name and Date:
Julie Nemecek, Ph.D.
I concur. December 17, 2018

David Bateman

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Julie Nemecek

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QUALITY ASSESSMENT

BIOPHARMACEUTICS

NDA: 208219-ORIG-1

Drug Product Name / Strength: Loteprednol Etabonate Ophthalmic Gel, 0.38%

Route of Administration: Ophthalmic

Applicant Name: Bausch & Lomb Incorporated

Review Recommendation: From the Biopharmaceutics perspective, NDA 208219 for Loteprednol Etabonate Ophthalmic Gel, 0.38%, is **adequate** and recommended for **approval**.

REVIEW SUMMARY

Submission: The Applicant is seeking approval for NDA 208219 for Loteprednol Etabonate Ophthalmic Gel, 0.38%, via 505(b)(1) route for the treatment of inflammation and pain following ocular surgery.

Review: The proposed product is a topical gel for ophthalmic application. No Biopharmaceutics related information was submitted in the application. No in vitro release testing (IVRT) was used/proposed for quality control of the proposed product. Per current practice, IVRT is not required for batch-to-batch quality control of the proposed semi-solid dosage form for topical use. However, IVRT could be required to support certain scale-up and post-approval changes (SUPAC). Therefore, the Applicant was recommended to develop an appropriate IVRT method and collect in vitro drug release data for the pivotal clinical study batches. The Applicant proposed to perform these studies post-approval. The Applicant's proposal is acceptable.

From a Biopharmaceutics perspective, NDA 208219 for Loteprednol Etabonate Ophthalmic Gel, 0.38%, is **adequate** and recommended for **approval.**

Primary Biopharmaceutics Reviewer:

Kaushalkumar Dave, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch 1
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer:

I agree with Dr. Dave assessment and recommendation

Jing Li, Ph.D.
Acting Biopharmaceutics Team Lead
Division of Biopharmaceutics-Branch 1
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSSESSMENT

1. LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	04/25/2018	Original NDA Submission
0005	07/06/2018	Quality/Response to Biopharmaceutics Information Request
0011	10/25/2018	Quality/Response to Biopharmaceutics Information Request

2. DRUG PRODUCT

The proposed drug product, Loteprednol Etabonate Ophthalmic Gel, 0.38%, is an (b) (4) sterile ophthalmic gel for topical administration. The composition of the proposed product is presented in Table 1.

Table 1: Composition of Loteprednol Etabonate Ophthalmic Gel, 0.38%

Component[1]	**Reference to Quality Standard**	**Function**	**Label strength: 0.38%**	
			Amount (mg/g fill)	**%(w/w)**
Loteprednol etabonate, (b) (4)	In-house	Active ingredient	(b) (4)	0.38%
Glycerin	USP/ Ph.Eur.	(b) (4)		(b) (4)
Propylene glycol	USP/ Ph.Eur.			
Sodium chloride	USP/ Ph.Eur.			
Benzalkonium chloride	NF/ Ph.Eur.	Anti-microbial agent		0.003%
Polycarbophil	USP	(b) (4)		(b) (4)
Hypromellose (b) (4) (b) (4)	USP			
Sodium hydroxide (b) (4)	NF/ Ph.Eur.	Alkalizing agent		
Poloxamer 407	NF	(b) (4)		
Edetate disodium dihydrate	USP/NF			
Boric acid	NF/ Ph.Eur.			
Water for injection	USP/ Ph.Eur.			
		Total		-

3. BRIDGING

There were no in-vitro and/or in-vivo bridging studies needed because:

- The composition of the clinical batch, registration batches, and the proposed commercial batches is the same;
- There was no change in the manufacturing site for the proposed product. The clinical and registration batches were manufactured at the same site as the proposed site for the commercial batches;
- There were no major changes in the manufacturing process in the scale-up.

However, as per the current practice in the Division of Biopharmaceutics, the Applicant was recommended (via a General Advice Letter dated 06/21/2018[1]) to develop a suitable in vitro release testing (IVRT) method for the proposed product and collect IVRT data for the clinical batch. In the response[1] (dated 07/06/2018), the Applicant acknowledged the FDA's recommendation regarding the development of an IVRT method that may be needed for bridging to support the approval of future post-approval changes that may potentially impact the efficacy and safety of the product. The Applicant stated that they have not developed and validated an IVRT methodology for the proposed product and the batches used in the pivotal clinical studies are already expired. The Applicant proposed to develop IVRT method to support the approval of certain scale-up and post-approval changes as outlined in the SUPAC-SS Guidance published by the FDA in May 1997[2], after the approval of the proposed Loteprednol Etabonate Ophthalmic Gel, 0.38%. Via an Information Request (dated 10/11/2018[3]), the Applicant was informed that their proposal to develop the in vitro release testing (IVRT) method after the approval of NDA 208219 is acceptable. The Applicant was also informed that if this NDA is approved, they should submit the 'IVRT Method Development/Validation Report' as a CMC Supplement proposing the addition of the IVRT method to the NDA (not for QC purpose), which can be used to support certain post approval changes per the SUPAC-SS Guidance[2]. In response (dated 10/25/2018[3]), the Applicant stated that the IVRT studies will be conducted post-approval and prior to any relevant/applicable changes as per the FDA's recommendation. The Applicant's response is adequate.

4. RECOMMENDATION

From a Biopharmaceutics perspective, NDA 208219 for Loteprednol Etabonate Ophthalmic Gel, 0.38%, is **adequate** and recommended for **approval.**

[1] Application 208219 - Sequence 0005 - Quality Information Amendment - Response to General Advice Letter dated 21 Jun 2018
[2] https://www.fda.gov/downloads/drugs/guidances/ucm070930.pdf
[3] Application 208219 - Sequence 0011 - Quality Information Amendment - Response to CMC IR dated 11 Oct 2018

Kaushalkumar Dave

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