CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208144Orig1s000

PRODUCT QUALITY REVIEW(S)

1.12.14 Environmental Analysis

Bausch & Lomb, a division of Valeant Pharmaceuticals North America LLC, hereby claims that the action requested of approval of this new drug application (NDA) for brimonidine tartrate ophthalmic solution, 0.025%, , qualifies for a categorical exclusion and therefore does not require the submission of a full environmental assessment per 21 CFR 25.31(b).

This is an additional brimonidine tartrate-containing drug product that will have little to no contribution to the aquatic or terrestrial environment, compared to the 1.0 PPB threshold outlined in 21 CFR 25.31(b). The calculation below is from the FDA *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications", July 1998*, and is used to estimate the potential concentration of the substance at the point of entry into the aquatic environment.

Basic assumptions

- Compound in use is brimonidine tartrate
- Quantity of active per proposed commercial and sample use is (b) (4) per year

The expected introduction concentration (EIC) of brimonidine tartrate into the aquatic environment is calculated as follows:

EIC Aquatic (PPB) = A*B*C*D

A = kg/year of product use

B = 1/liters per day entering publicly owned treatment works (POTW) (1.214 X 10^{11} liters per day standard)

C = year/365 days

D = 10^{9} µg/kg (conversion factor)

Brimonidine tartrate calculation:

A = (b) (4)

(b) (4)

B = (b) (4)

C =

D =

Result: A*B*C*D = (b) (4)

This result is well below the 1.0 PPB threshold outlined in 21 CFR 25.31(b). Therefore, a categorical exclusion from further environmental assessment under 21 CFR 25 is requested.

(b) (4)

(b) (4)

3/13/15

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/s/

MELISSA V CHHANGTE
01/02/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Executive Summary Review #2 Addendum

Date: December 30, 2017
From: **Swapan K De, Ph.D.**
CMC Team Lead, CDER/OPQ/ONDP/DNDP II/Branch VI
Application Technical Lead (NDA 208144)

Subject: **Addendum to NDA 208144 executive summary review (**brimonidine tartrate ophthalmic solution 0.025%)

1. Proprietary Name: Following a T-con dated November 07, 2017 between FDA and Bausch & Lomb regarding safety concern and confusion of the proposed proprietary name Luminesse™ with another product, the applicant requested withdrawal of the name Luminesse™ on 11/14/2017. The applicant has submitted a proprietary name (Primary name: (b) (4), Alternate: Lumify) review document on 11/16/2017. The Agency considered the document as a complete submission, thus set up a user fee goal date, February 14, 2018 to review the request for proprietary name.
2. Labeling: Discard Statement: OPQ quality review (dated 11/6/17) granted the proposed labeling storage statement "discard 120 days after opening the bottle" based on the submitted in-use stability study conducted for a period of 120 days. The study results show that the multi-dose ophthalmic product remains within specifications when opened and used as indicated for the study period. DMEPA (review dated 11/8/17) recommended to keep the discard statement to the PDP. However, DTOP (Division of Transplant and Ophthalmology Products) clinical review (dated 11/27/17) advised that the discard statement "should not be retained". The basis for the recommendation was that "the data does not support any differences between the in-use stability data and the un-opened standard storage condition stability data". OPQ agrees with the DTOP statement up to 120 days, but advises that no data are available for in-use conditions after 120 days. The subject was discussed on November 20, 2017 and OPQ microbiology review was updated with an addendum (November 27, 2017) to state that "from a microbiological perspective, the risk to the patient due to microbial contamination after product opening is considered low" based on submitted data and to recommend "that standard labeling practices concerning discarding opened multi-dose ophthalmic products be followed." Multi-dose ophthalmic over-the-counter products such as Refresh Liquigel and Optive (90 days) as well as Blink (45 days) include a discard statement, while others such as Visine do not.

3. Labeling: Storage Statement: OPQ quality review (dated 11/6/17) recommended strengthening the storage statement by adding a warning against storage at high temperatures e.g. "discard if the product if stored at any temperature above 30°C (86°F)". The recommendation was based on changes in the pH, osmolality and concentration of the drug product seen in stability results and was made to assure that the quality of the product remained within specifications similar to the reference listed drug (RLD) when used by the consumer in an over-the counter setting. However, DTOP (Division of Transplant and Ophthalmology Products) clinical review (dated 11/27/17) advised that the warning statement "is not warranted from a clinical prospective" since "changes in pH and osmolality do not reach levels that are likely to affect the safety or efficacy of the drug product". Thus, OPQ defers decision regarding the discard statement to the DNDP labeling team.

Swapan De

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 27 November 2017

TO: **Thao Vu**
Regulatory Health Project Manager
CDER/OPQ/OPRO

FROM: **Elizabeth Bearr, Ph.D.**
Microbiologist
CDER/OPQ/OPF/Division of Microbiology Assessment
(240) 402-4467

THROUGH: **Erika Pfeiler, Ph.D.**
Quality Assessment Lead (Acting)
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: Addendum to NDA 208144 microbiology review N208144MR01.doc
Submission Date: 11/17/2017
Drug Product: brimonidine tartrate ophthalmic solution 0.025%
Applicant: Bausch & Lomb, a wholly-owned subsidiary of Valeant Pharmaceuticals International Inc.

The Division of Nonprescription Drug Products (DNDP) requested that the Division of Microbiology Assessment provide an addendum to the microbiology review of NDA 208144 to address whether the labeling statement "Discard remaining product 120 days after opening" should remain or be removed from the final product label. From the microbiological perspective, the risk to the patient due to microbial contamination after product opening is considered low based on the following data:

- USP <51> testing (AET) was performed on the drug product formulated with preservative levels ranging from (b) (4)%. The drug product formulated at (b) (4)% of the preservative label claim met the USP <51> criteria for adequate preservative effectiveness for a Category 1 product. It is expected that the preservative content would need to degrade by more than (b) (4)% before a contamination event led to excessive microbial growth.
- An in-use study was conducted wherein 2 drops of the drug product were dispensed every other day for 121 days. The drug product was capable of passing AET after 121 days of simulated use.

MEMORANDUM

- AET was performed on drug product stability samples stored unopened at 25ºC for 24 months (i.e. expiry for the "worst case" 7.5 mL drug product) and the samples met the acceptance criteria.

Based on these data, DMA recommends that standard labeling practices concerning discarding opened multi-dose ophthalmic products be followed.

END

Elizabeth Bearr

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Erika Pfeiler

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EXECUTIVE SUMMARY

NDA 208144
Review # 1
Recommendation: APPROVAL

Drug Name/Dosage Form	**Luminesse™ (brimonidine tartrate ophthalmic solution)**
Strength	0.025%
Route of Administration	Topical ophthalmic
Rx / OTC Dispensed	OTC
Applicant	Bausch & Lomb, a wholly-owned subsidiary of Valeant Pharmaceuticals International Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (SD 0000)	31 Mar-2015	
Amedment (SD 0005)	19-May-2017	
Resubmission(SD 0016)	27-Feb-2017	ONDP/OPF
Amendment (SD0019)	28-April-2017	ONDP/OPF
Amendment (SD0025)	02-Aug-2017	ONDP/OPF
Amendment (SD0026)	02-Oct-2017	ONDP
Amendment(SD0028)	16-Oct-2017	ONDP
Amendment(SD0029)	31-Oct-2017	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Anne Marie Russell, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Tarun Mehta	OPF/DPAII/BranchVI
Microbiology	Elizabeth Bearr , Ph.D.	OPF/DMA/MABI
Facility	Donald L Lech	OPF/DIA/IABIII
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMF

	TYPE			STATUS[1]	REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	21-Jan-2013	Active	Sufficient data in the application.
	Type III			18-Jun-2013	Active	The DMF and the components have been reviewed in by Dr. Yushi Feng, PhD. (23- Aug-2016), and were found to be adequate.
	Type III			12-Dec-2014	Active	Sufficient data in the application.
	Type III			21-Jan-2013	Active	Sufficient data in the application.
	Type III			28-Jun-2013	Active	The DMF and the components have been reviewed in by Dr. Joel Hathaway, PhD. (04- May-2016), and were found to be adequate.
	Type III			24-Jul-2014	Active	The DMF and the components have been reviewed in by Dr. Ping Jiang-Baucom, PhD. (11-May-2015), and were found to be adequate.

[1] Adequat st, Deficient, or N/A (There is enough data in the applicatio be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-613	Alphagan (Brimonidine Tartrate Opthalmic Solution 0.2%)
IND	108524	Brimonidine Tartrate Opthalmic Solution 0.025%
ANDA	076260	Brimonidine Tartrate Opthalmic Solution 0.20%

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			

Table of Contents

Executive Summary (NDA-208144)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the application the drug substance, drug product, process, microbiology and facility sections are reviewed and found adequate to support the approval of the application. The drug product has been granted a shelf life of 15 months for the 2.5mL fill and 24 months for the 7.5mL fill product configuration. In addition, 120 day in-use period is granted (i.e. once the bottle is opened it should be discarded after 120 days).

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

II. Summary of Quality Assessments;

The application is a resubmission following a "refuse to file" letter from the Agency dated May 29, 2015 due to lack of post-marketing data critical for an adequate safety review of the product for proposed use in an over-the counter (OTC) consumer population. The application is resubmitted on February 27, 2017.

Quality information for the drug substance, drug product, manufacturing process, microbiology and facility are included in the quality overall summary section and is acceptable. Some basic information is shown below.

1. Drug Substance [USAN Name] Quality Summary

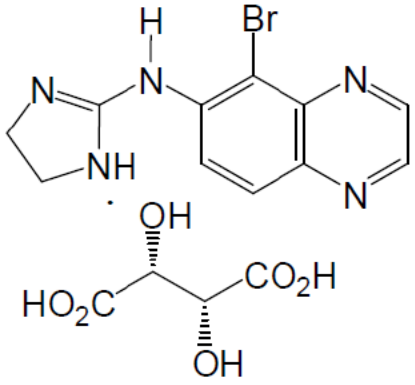
Chemical Name or IUPAC Name/Structure: 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine L-Tartrate.

USAN: Brimonidine Tartrate

Formula: ($C_{11}H_{10}BrN_5.C_4H_6O_6$).

CAS Number 70359-46-5

MW= 442.22 g/mol



The approved suppliers of Brimonidine tartrate is [redacted] DMF [redacted] has been reviewed at least 18 times, most recently on 3/1/2017 by Dr. Simon Peng and found adequate. LoA dated 12/4/2014 is provided in the original NDA (see drug substance review).

Specifications follow current compendial monographs. Specifications include description, identification (IR and HPLC RT), solution pH [redacted], LOD (NMT [redacted]%), residue on ignition (NMT [redacted]%), heavy metals (NMT [redacted]), assay ([redacted]% [redacted], related substances ([redacted] NMT [redacted]%, any other impurity NMT [redacted]% and total impurities NMT [redacted]%), residual solvents ([redacted] NMT [redacted]), ([redacted]% of label claim or [redacted]% [redacted] optical rotation [redacted] and bioburden (total aerobic count NMT [redacted] yeast/mold count NMT [redacted] absence of *S. aureus, P. aeruginosa, E. coli, Salmonella spp., B. cepacian*.

Brimonidine tartrate [redacted] is stored at [redacted] and a [redacted] month re-test period is assigned based on stability data from long term and accelerated storage conditions.

A. Drug Product [Established Name] Quality Summary

1. Strength: 0.025%

2. Description/Commercial Image:

The proposed OTC drug product is Luminesse™ (0.025% brimonidine tartrate ophthalmic solution). It will be marketed as a vasoconstrictor for the relief of eye redness due to minor eye irritations in adults and children 5 years of age and older. Dosing regimen is 1 drop in affected eye(s) every 6-8 hours, no more than 4 times daily. The product will be available in two configurations 2.5 mL and 7.5 mL fill volume and these volumes (2 configurations) will also be used for physician samples.

3. Summary of Product Design

The applicant has used a similar process for their approved marketed drug product (ANDA 076260), Brimonidine Tartrate Opthalmic Solution, 0.2% and referred the application for detailed manufacturing process.

4. List of Excipients:

Benzalkonium Chloride, Boric Acid, Calcium Chloride Dihydrate, Glycerin, Potassium

6. **Container Closure**:

The product is packaged in a 10mL round white low-density polyethylene (LDPE) bottle fitted with a (b) (4) dropper tip and closed with a child-resistant cap composed of a purple (b) (4) outer and a (b) (4) (b) (4) inner closure. Primary packaging components are tested and sterilized with (b) (4)

The bottle is fitted with a clear tamper resistant neckband and an adhesive label, then packaged in a carton.

7. **Expiration Date & Storage Conditions**

Proposed expiry of **15 months for the 2.5mL fill** and **24 months for the 7.5mL** fill product is acceptable and supported by the real-time stability data from for 3 registration lots for each fill, plus one clinical lot and one commercial lot for each fill (See attached: drug product review).

Based on in-use stability data for both 2.5 mL and 7.5 mL configurations, 120 day in-use period is granted. "Discard 120 days after opening the bottle" is suggested to be in the label.

The storage statement will be written as "Store at 15° (b) (4) 25°C (59°F (b) (4) 77°F)".

8. **List of co-packaged components: None**

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Luminesse™
Non Proprietary Name of the Drug Product	Brimonidine Tartrate Opthalmic Solution /0.025%
Non Proprietary Name of the Drug Substance	Brimonidine Tartrate
Proposed Indication(s) including Intended Patient Population	Relieve redness of the eye due to minor eye irritations. Adults and children ≥5 years
Duration of Treatment	1 drop in the affected eye(s) every 6-8 hours up to 4 times/day
Maximum Daily Dose	See "duration of treatment".
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification: Not applicable (BCS class is determined only when applicant proposed the product as BCS Class I.
   - Drug Substance:

- Drug Product:

2. Biowaivers/Biostudies (For NDA only)
   - Biowaiver Requests: No
   - PK studies: N/A
   - IVIVC: No

D. Novel Approaches

E. Any Special Product Quality Labeling Recommendations

Established name of the drug product remains "Brimonidine tartrate ophthalmic solution" as approved in the prescription ANDA 076260, although based on current FDA guidance ("Naming of drug products containing salt drug substances guidance for Industry"-June 2015) and USP salt policy of the active moiety, the established name should contain the active moiety in neutral form without the name of salt. However, to avoid confusion with the prescription product the established name for the OTC product is accepted as proposed "Brimonidine tartrate ophthalmic solution".

Luminesse™

(brimonidine tartrate ophthalmic solution 0.025%**)**

Based on stability data following labeling recommendation needs to be discussed.

- Warning to discard the product if the product was stored at any temperature above 30°C (86°F)
- Discard 120 days after opening the bottle.

F. Life Cycle Knowledge Information (see table below)

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipmen	2	2	2	8	Controlled through specifications.
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipmen	2	2	2	8	Controlled through specifications (USP)
Particulate matter	• Formulation Container closure • Raw materials • Process parameters	3	2	2	12	Meets USP, light obscuration.
Sterility	• Formulation • Raw materials • Process	2	3	2	8	Meets USP<61>.

	• Scale/equipment • Site					

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead S

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MICROBIOLOGY

Product Background: -

NDA: 208144

Drug Product Name / Strength: Luminesse (Brimonidine Tartrate Ophthalmic Solution) / 0.025%

Route of Administration: Topical ophthalmic

Applicant Name: Bausch & Lomb, a wholly-owned subsidiary of Valeant Pharmaceuticals International Inc.

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

Method of Sterilization: (b) (4)

Review Recommendation: The submission is recommended for approval on the basis of sterility assurance.

Review Summary: The drug product is (b) (4)

(b) (4)

List Submissions being reviewed: 3/31/2015, 02/27/2017, 04/28/2017, and 08/02/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

Supporting/Related Documents: N/A

Remarks Section: The application was originally submitted on 03/31/2015. The agency refused to file the application (RTF letter archived on 05/29/2015). The applicant requested a Type A meeting, which was held on 07/29/2015, and a list of DMA comments that captured deficiencies in the 03/31/2015 submission were issued with the Preliminary Meeting Comments on 07/28/2015. The application was resubmitted on 02/27/2017. DMA comments were conveyed in the filing communication on 4/13/2017. The applicant's submission dated 04/28/2017 is in response to deficiencies issued in the filing communication dated 04/13/2017. The applicant's submission dated 08/02/2017 is in response to the Agency's Information Request dated 07/26/2017.

S Drug Substance – N/A, non-sterile

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product is a sterile, aqueous-based solution for topical ophthalmic administration, pH (b) (4), containing 0.025% brimonidine tartrate, 7.5 mL and 2.5 mL fill in 10 mL multi-dose bottles.

- Drug product composition –

Ingredient	mg
Brimonidine Tartrate	0
Glycerin	(b) (4)
Sodium Borate Decahydrate	
Boric Acid	
Potassium Chloride	
Calcium Chloride Dihydrate	
Sodium Chloride	
Benzalkonium Chloride (BAK), (b) (4)	
(b) (4) Sodium Hydroxide[c]	
Hydrochloric Acid	
Water for Injection	

a (b) (4)

b

c (b) (4)

- Description of container closure system –

Configuration	Component		
0.025%, 7.5 mL or 2.5 mL fill	Bottle		(b) (4)
	Tip	(b) (4)	
	Cap		

Reviewer's Assessment: Adequate

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

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(eCTD seq #0000: Section 3.2.P.2.5 Microbiological Attributes, pp. 3-5)

The container/closure system used for validation was the same as the drug product. Container closure integrity was tested by the microbial immersion method. Integrity test units were selected from passing (negative for growth) media fill simulation samples. Representative process simulation media fill test units were selected from across the entire fill. Positive controls were prepared by adding a sanitized insulated wire with a minimum 24 gauge to each of 5 units such that the wire would interfere with the bottle/tip seal and the tip/closure seal and the units were reassembled. Five growth promotion controls were prepared and each consisted of a unit inoculated with < 100 CFU/0.1 mL of

the *B. diminuta* challenge organism. The growth promotion units were not exposed to the pressure and vacuum. Five negative control units were not immersed in the challenge organism, but were exposed to pressure and vacuum. Test units and positive controls were submerged in a *B. diminuta* suspension (10^6 CFU/mL) for 20 minutes at room temperature. Following immersion, the units were placed in a pressure system and 5 psi of pressure was applied for 5 minutes followed by a vacuum of ~5" of mercury for 5 minutes. The challenge units and all controls were incubated at 32.5° ± 2.5°C for NLT 7 days. Containers were then examined for signs of microbial growth (turbidity).

Acceptance Criteria:

- No *B. diminuta* isolated from any challenged media container.
- All 5 breached controls are positive for growth.
- All 5 growth promotion controls are positive for growth.
- All negative controls are negative for growth.

Results: The results of the study provided below meet all acceptance criteria.

Sample	# Positive/ # Tested
Test Units	0/110
Positive Control	5/5
Growth Promotion	5/5
Negative Control	0/5

Reviewer's Assessment: Adequate

The applicant provided adequately validated the integrity of the proposed container-closure system.

Antimicrobial Effectiveness Testing

(Section 3.2.5.1, pp. 1-2)

The procedure used for antimicrobial effectiveness testing was performed according to USP <51>. The drug product specification requires (b) (4)% of (b) (4) (b) (4) label claim for release and (b) (4)% of label claim for stability. The AET evaluated (b) (4) levels ranging from 0 – 100%. Lot #: BCL462-016A, BCL462-016G, BCL462-016F, BCL462-016E, BCL462-016D, BCL462-016C contained 0%, 10%, 25%, 50%, 75%, and 100% (b) (4) respectively.

Results: The actual plate counts were not provided; however, the applicant states that the test articles were inoculated with a minimum of 1.0 x 10^5 CFU/mL. The AET results for lot #BCL462-016G containing (b) (4)% of (b) (4) label claim are provided below.

Organism	Log reduction in Plate Counts			
	Day 0	Day 7	Day 14	Day 28
A. niger (ATCC 16404)	N/A	>4.66	>4.66	>4.66
C. albicans (ATCC 10231)	N/A	>5.23	>5.23	>5.23
E. coli (ATCC 8739)	N/A	>5.04	>5.04	>5.04
S. aureus (ATCC 6538)	N/A	>4.93	>4.93	>4.93
P. aeruginosa (ATCC 9027)	N/A	>4.95	>4.95	>4.95

All lots met the USP <51> criteria for adequate preservative effectiveness for a Category 1 product except for the lot with no (b) (4)

Reviewer's Assessment: Adequate

The AET results support the effectiveness of the minimum release and stability specifications.

P.3 Manufacture

P.3.1 Manufacturers

Bausch & Lomb, Inc., 500 Hidden River Parkway, Tampa, FL 33637
Responsible for: drug product manufacturing, packaging, labeling, in-process testing, analytical and microbiological release testing for product and excipients, and stability testing occurs at this location.

Drug product

Release/stability testing (as applicable)

Bausch & Lomb, Inc., 1400 N. Goodman Street, Rochester, NY 14609
Alternate facility for analytical and microbiological release and stability testing.

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

(eCTD seq #0000: Section 2.3.P, pp. 29-33; Section 3.2.P.2., Manufacturing Process Development, p. 12)

The overall manufacturing operation information reviewed below includes the information provided in the initial submission dated 3/31/2015. The review also covers the information provided in the applicant's resubmission dated 02/27/2017 in response to

(b) (4)

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