CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209353Orig1s000

PRODUCT QUALITY REVIEW(S)

Integrated Quality Assessment (IQA) for NDA 209353

Office of Pharmaceutical Quality (OPQ)

Executive Summary for NDA 209353

APPEARS THIS WAY ON ORIGINAL

Recommendation:

From the OPQ perspective, this 505(b)(1) NDA is ***not*** deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

NDA 209353
Review # 1

Drug Name/Dosage Form	ALTRENO™ (tretinoin) Lotion, for Topical Use
Strength	0.05% (w/w)
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Dow Pharmaceutical Sciences, Inc. Sean Humphrey Suite C, 1330 Redwood Way Petaluma, CA 94954
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	10-27-2017	All
Amendment	12-20-2017	Facilities
Amendment	12-21-2017	Biopharmaceutics
Amendment	01-16-2018	Drug product manufacturing process
Amendment	04-02-2018	Drug product, Drug product manufacturing process and Quality microbiology
Amendment	06-04-2018	Drug product (carton and container labels)
Amendment	06-08-2018	Drug product manufacturing process

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeffrey Medwid	Branch II/Division of New Drug API
Drug Product	Zhengfang Ge	Branch V/Division of New Drug Products II
Process	Zhao Wang	Branch V/Division of Process Assessment III
Microbiology	Daniel Schu	Branch III/Division of Microbiology Assessment
Facility	Zhao Wang	Branch V/Division of Process Assessment III
Biopharmaceutics	Sandra Suarez	Branch III/Division of Biopharmaceutics
Regulatory Business Process Manager	Bamidele (Florence) Aisida	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b)(4)	Type II		(b)(4)	1	March 20, 2018	Adequate
	Type III			4	N/A	N/A
	Type IV			4	N/A	N/A
	Type IV			4	N/A	N/A

Action codes for

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

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
End-of-Phase 2 Meeting Minutes	(b)(4)	Discussions of development plan for tretinoin lotion.
Pre-NDA Meeting Minutes	IND 126753	Discussions of the content and format of the proposed NDA submission.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----	N/A	----	----
Pharmacology/Toxicology	----	N/A	----	----
CDRH	----	N/A	----	----
Clinical	----	N/A	----	----

Other	----	N/A	----	----

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility (OPF) has issued an "Acceptable" recommendation for the facilities involved in this application.

However, the issues on labels/labeling are not completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved (See the List of Deficiencies on p. 18).

II. Summary of Quality Assessments

A. Product Overview

The NDA of Altreno (tretinoin) lotion, 0.05% for topical use is submitted as a 505(b)(1) application by Dow Pharmaceutical Sciences, Inc. (a subsidiary of Valeant Pharmaceutical International). The following applications are cross-referenced for this 505(b)(1) application: NDA 022770 [Atralin (tretinoin) Gel, 0.05%], NDA 020475 [Retin-A Micro (tretinoin) Gel, 0.1%, 0.08% and 0.04%], NDA 017522 [Retin-A (tretinoin) Cream, 0.05%], NDA 021108 [Renova (tretinoin) Cream, 0.02%] and NDA 019963 [Renova (tretinoin) Cream, 0.05%].

The indication and recommended dose of the drug product are summarized in the following Table.

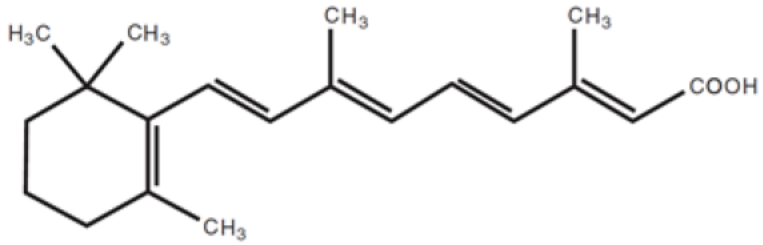
Proposed Indication(s) including Intended Patient Population	ALTRENO Lotion is indicated for the topical treatment of acne vulgaris.
Duration of Treatment	Long term
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The active pharmaceutical ingredient (API) in ALTRENO lotion, 0.05% is tretinoin, which is a retinoid.

The chemical name for tretinoin is all-trans (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. The chemical structure of tretinoin is:



It has a molecular formula of $C_{20}H_{28}O_2$ and a molecular weight of 300.44 g/mol. Tretinoin is a yellow to yellow-orange powder. It is very sparingly soluble in water. At 20°C, it has a solubility of 7.5 g in 100 mL chloroform, 0.4 g in 100 mL ethanol, 0.6 g in 100 mL isopropyl alcohol, 0.3 g in 100 mL isopropyl myristate. Tretinoin (b) (4) polymorphic form (b)(4) forms.

The drug substance is manufactured by (b)(4) (b)(4) Detailed CMC information of tretinoin drug substance for this NDA is referred to DMF (b)(4)

DMF (b)(4) was reviewed by Dr. Jeffrey B. Medwid on March 20, 2018 and found adequate in supporting the approval of this NDA. The review on the CMC information of the drug substance in the NDA has also been conducted by Dr. Jeffrey B. Medwid. The NDA is recommended for **approval** from the drug substance perspective (See **CHAPTER I: Review of Drug Substance**).

Drug Product

The drug product, ALTRENO lotion, is a topical lotion, which contains 0.05% (w/w) tretinoin. The inactive ingredients used in the drug product include: benzyl alcohol, butylated hydroxytoluene, carbomer copolymer type B (Pemulen TR-1), carbomer homopolymer type A (Carbopol 981), glycerin, methylparaben, mineral oil (b) (4) octoxynol-9, purified water, sodium hyaluronate, soluble collagen and trolamine. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (sodium hyaluronate and (b) (4) collagen) are used in the applicant's approved Atralin gel and are controlled to the same quality standards as in the approved drug product. The (b)(4) octoxynol 9 is purchased, but tested to ensure conformance with the current NF monograph except for the (b) (4)

test. The drug product is packaged as nominal 3 g and 45 g fill sizes in a blind end aluminum tube wit [redacted] and [redacted] cap. The tubes with 3 g filling are the proposed physician samples. The applicant provided sufficient information to demonstrate the safe use of the container/closure system.

The revised final specification for ALTRENO lotion is deemed adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. The long-term (25°C/60%RH) stability data up to 18 months, intermediate (at 30°C/65%RH) stability data for 12 months and accelerated (40°C/75%RH) stability data for 6 months are provided for the three registration batches of the drug product (packaged in 3g and 45g package sizes) produced a [redacted] scale in the NDA submission. The stability data submitted are sufficient to support the proposed expiration dating period of 24 months when stored at room temperature. The results of in-use studies support that the product can be continuously used over the course of 12 weeks with no undesirable trends to physical and chemical characteristics. The drug product can withstand repeated freezing and thawing, and cold-warm cycling stressed conditions. The estimated EIC (expected introduction concentration) for the drug substance is well below 1 ppb. The claim of categorical exclusion is acceptable per 21 CFR 25.31(b).

The drug product is recommended for **approval** from the drug product perspective. The recommended expiration dating period of the drug product is 24 months. The review on the CMC information of the drug product has been conducted by Dr. Zhengfang Ge (See **CHAPTER II: Review of Drug Product**).

Labeling and Labels

The sections of the Prescribing Information related to CMC, and container and carton labels of the drug product of the NDA have been reviewed by Dr. Zhengfang Ge. Labeling and label issues have not been resolved satisfactorily as of this review (See **CHAPTER III: Review of Labeling and Labels**).

Drug Product Manufacturing Process

The bulk drug product is prepared b [redacted] ingredients, and [redacted]. The active ingredient, tretinoin, is [redacted] in the lotion. The manufacturing process of the tretinoin lotion includes the following steps:

[redacted]

(b)(4)

[redacted]

(b) (4)

The batch formula, manufacturing process parameters, and in-process controls are deemed adequate to ensure the robustness of the drug product manufacturing process. The proposed manufacturing process, batch size (b) (4), and facility for intended commercial batches are the same as those used for manufacturing the registration batches of the drug product. The NDA is recommended for **approval** from the perspective of drug product manufacturing process. The review on the drug product manufacturing process has been conducted by Dr. Zhao Wang (See **CHAPTER IV: Review of Drug Product Manufacturing Process**).

Biopharmaceutics

The applicant is seeking for approval of ALTRENO Lotion 0.05% under this NDA. The API, tretinoin, is (b)(4) in the lotion. Particle size distribution of the API is deemed critical for the in vitro and in vivo performance of the drug product. Particle size distribution test is included in (b) (4) drug product specifications.

The Applicant did not include IVRT (in vitro release test) in the drug product specification. Nevertheless, the Applicant was advised during the review cycle to consider the development and validation of a robust and reproducible IVRT method (b)(4)

(b)(4)

(b)(4)

The manufacturing site for the clinical and commercial product is the same, which is Valeant Pharmaceuticals International, in Quebec, Canada. The assurance of the quality of the drug product relies on drug product specifications (other than in vitro release testing) and in process controls characteristic of topical lotion formulation.

The NDA is recommended for **Approval** from the perspective of Biopharmaceutics. The review on Biopharmaceutics of the drug product of the NDA has been conducted by Dr. Sandra Suarez (See **CHAPTER V: Review of Biopharmaceutics**).

Quality Microbiology

The drug product is a non-sterile lotion containing 0.05% tretinoin. Antibacterial preservatives, methylparaben and benzyl alcohol, are included in the drug product formulation.

The antimicrobial effectiveness testing (AET) per USP <51> was performed with drug product lots formulated with both preservatives a (b) (4) (b)(4) of the label claim. Method suitability testing was performed with modified Tryptic Soy Broth. Log reduction data for the drug product lots formulated with both preservatives at all four concentrations were provided and met USP <51> acceptance criteria for Category 2 products. All challenge bacteria demonstrated a greater than (b) (4) log reduction at 14 days and no increase at 28 days. All samples inoculated with *C. albicans* and *A. brasiliensis* demonstrated no increase at 14 and 28 days.

Microbial testing for Total Aerobic Microbial Count, Total Combined Yeast/Mold Count, Absence of *S. aureus* and *P. aeruginosa*, and Absence of *B. cepacia* complex (BCC) is included in the drug product specification. Method suitability testing was performed for microbial enumeration per USP <61> and specified microorganisms (i.e., *S. aureus* and *P. aeruginosa*) per USP <62> with acceptable results. The results of validation study for the method used for routine evaluation for the absence of BCC were provided in the submission. Routine testing for BCC will require 24 - 48 hour incubation at 30 - 35ºC for enrichment broth (TSB-M (modified Tryptic Soy Broth)) and 48 - 72 hour incubation at 30 - 35ºC for the subsequent subculture onto BCSA (*Bulkholderia Cepacian* Selective Agar) plates.

Assays of methylparaben and benzyl alcohol are included in the drug product specification. AET was performed at initial and 6 months for stability samples stored at 40ºC/75%RH and at initial and 12 months for stability samples stored at 25ºC/60%RH and 30ºC/65%RH. Samples at all test conditions and time points passed AET requirements. Microbiological testing (i.e., TAMC; TYMC; absence of *S. aureus*, *P. aeruginosa*, and BCC) is included in the post-approval stability protocol per Agency's request.

The NDA is recommended for **Approval** from the perspective of quality microbiology. The review on microbiology controls of the drug product of the NDA has been conducted by Dr. Daniel Schu (See **CHAPTER VI: Review of Quality Microbiology**).

Facilities

The status of the facilities related to the **drug substance** manufacture and testing is summarized in the following Table:

Status of Facilities Related to Drug Substance Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
(b)(4)			Approve based on profile
			Approve based on profile

The status of the facilities related to the **drug product** manufacture and testing is summarized in the following Table:

Status of the Facilities Related to the Drug Product Manufacture and Testing

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
Valeant Pharmaceuticals International, Inc. 2150 St. Elzear Boulevard West Laval, Quebec, Canada H7L 4A8	3002807186	Manufacturing, packaging, labeling, release and stability testing Profile Code: **OIN**	Approve base on file review
Dow Pharmaceutical Sciences 1330 Redwood Way Petaluma, California 94954	1000135370	Alternate release and stability testing facility Profile Code (b)(4) (b)(4)	Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			No Further Evaluation (NFE)

All the facilities are deemed acceptable in their identified functions and responsibilities to support the **approval** of NDA 209353. The facility review of the NDA has been conducted by Dr. Zhao Wang (See **CHAPTER VII: Review of Facilities**).

C. Special Product Quality Labeling Recommendations
N/A

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies (Attachment II)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessments - NDA

a) Drug Product

Final Risk Assessment for NDA 209353 [ALTRENO™ (tretinoin) lotion, 0.05% for topical use]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay Tretinoin and its degradation products	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	An HPLC method is used to quantitate the drug content (tretinoin assay) and its degradation products in the drug product at release and during stability studies. The results of tretinoin assay and degradation products showed no significant change at various test conditions (long-term for 18 months, intermediate and accelerated tests; freeze-thaw cycles and cold-warm cycles) during stability studies.
Assay – methylparaben	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	2	18	An HPLC method is used to quantitate the level of methylparaben (a pereservative) in the drug product at release and during stability studies. The assay results for methylparaben ranged from (b)(4)% of the target level for stability samples packaged in both fill sizes (3 g and 45 g) and stored at various test conditions during stability studies. Results of antimicrobial effectiveness testing (AET) per USP <51> indicated that log reduction of methylparaben (b)(4)% of the target concentration met USP <51> acceptance criteria for Category 2 products.
Assay – Benzyl Alcohol	• Formulation • Raw materials	3	3	2	18	An HPLC method is used to quantitate the level of benzyl alcohol (a pereservative) in the drug product at release and during stability studies.

	• Process parameters • Scale/equipment • Site					The assay results for benzyl alcohol ranged from (b)(4)% of the target level for stability samples packaged in both fill sizes (3 g and 45 g) and stored at various test conditions during stability studies. Results of antimicrobial effectiveness testing (AET) per USP <51> indicated that log reduction of benyl alcohol (b)(4)% of the target concentration met USP <51> acceptance criteria for Category 2 products.
Assay – Butylated Hydroxytoluene	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	2	18	An HPLC method is used to quantitate the level of butylated hydroxytoluene (b)(4) in the drug product at release and during stability studies. The assay results for butylated hydroxytoluene ranged from (b)(4)% of the target level for stability samples packaged in both fill sizes (3 g and 45 g) and stored at various conditions during stability studies. The acceptance criterion set for butylated hydroxytoluene is between (b)(4) and (b)(4)%.
Uniformity in containers – Tretinoin	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	The test is conducted per USP <3> at release and during stability studies. (b)(4) (b)(4) However, all tretinoin assay results of the stability samples met the uniformity requirements for (b)(4) of the label claim with a maximum difference within each tube of not more than (NMT) (b)(4)%.

Particle Size of Tretinoin	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	3	27	(b)(4) The results of stability studies indicated that the particle size of the API meet the acceptance criteria of not less than (NLT) (b)(4) and NLT (b)(4) (b)(4) No trending was observed during stability studies.
(b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	(b) (4) of the lotion of the stability samples ranged from (b)(4) for (b)(4) and from (b)(4) for (b)(4) at various storage conditions. (b) (4) showed little variability and no significant trending during stability studies.
Microbial Testing **Total Aerobic Microbial Count, Total Combined Yeast/Mold Count, Absence of *S. aureus* and *P. aeruginosa*, Absence of *B. cepacia* complex (Bcc)**	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	2	3	18	Microbiological examination tests are conducted per USP <61> and USP <62> at release only. An in-house method is used to test *Bulkholderia Cepacia* Complex (Bcc) in the drug product. All stability batches tested at various intervals after 12 months storage at 25°C/60%RH (long-term) and 30°C/65%RH (intermediate) and 6 months at 40°C/75%RH (accelerated) conditions met the acceptance criteria for USP antimicrobial effectiveness test requirements.
pH	• Formulation • Raw materials	3	2	3	18	The pH of the drug product is monitored at release and during stability studies. The pH values ranged from (b)(4) for stability

	• Process parameters • Scale/equipment • Site					samples packaged in both fill sizes (3 g and 45 g) and stored at various storage conditions. No significant change and little variability in pH value was observed for the stability batches during stability studies.
Viscosity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	4	3	3	36	Viscosity of the drug product is monitored at release and during stability studies. Decrease in the viscosity values was observed during stability studies. This trend was more pronounced for samples in the 3 g fill size at elevated temperatures.
Minimum Fill	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	3	12	The test is performed per USP <755> and is only conducted at release of the drug product.
Package Integrity	• Formulation • Container components • Process parameters	2	3	3	18	Visual check. This test is only performed during stability studies. No deterioration was observed on the stability samples of all testing conditions during stability studies.

RPN: Risk Priority Number

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{bmatrix} D$$

Low Risk- RPN ≤ 25

Moderate Risk - $25 <$ RPN ≤ 60

High Risk - RPN > 60

ATTACHMENT II: List of Deficiencies

A. For the Prescribing Information

Section 11 should be revised as follows:

1. The Proprietary name and established name should be revised to "Altreno (tretinoin) Lotion" in the beginning of the paragraph.

2. Delete (b)(4) in the inactive ingredients as it is (b)(4) as (b)(4)

B. For the Container/Carton Labels

1. Delete (b)(4) in the inactive ingredients as it is (b) (4) as (b)(4)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead's Assessment and Signature

From the OPQ perspective, the NDA is not deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
6/26/2018

Yichun Sun

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Moo Jhong Rhee

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CHAPTER III: Review of Labeling and Labels

LABEL FOR NDA 210566

I. PI

1. Highlights of Prescribing Information

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	ALTRENO (tretinoin)	**Adequate**
Dosage form, route of administration	lotion, for topical use	**Adequate**
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	lotion, 0.05% Each gram of ALTRENO Lotion contains 0.5 mg (0.05%) tretinoin	**Adequate**

This section is adequate

2. *Section 2 Dosage and Administration*

(b)(4)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	For topical use only. Not for ophthalmic, oral, or intravaginal use. (b)(4)	**Adequate** **This section is similar to the approved Atralin gel**

This section is adequate

3. *Section 3 Dosage Forms and Strengths*

Lotion, 0.05%

Each gram of ALTRENO Lotion contains 0.5 mg (0.05%) tretinoin in an opaque, pale yellow topical lotion.

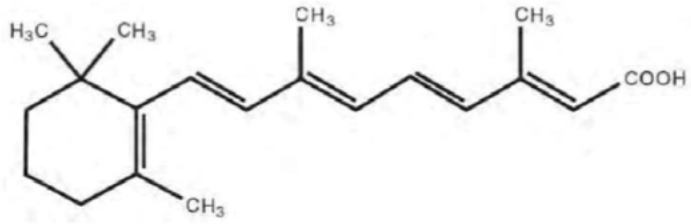
Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	lotion	**Adequate**
Strengths: in metric system	0.05%. Each gram of ALTRENO Lotion contains 0.5 mg (0.05%) tretinoin	**Adequate**
Active moiety expression of strength with equivalence statement (if applicable)	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	opaque, pale yellow topical lotion	**Adequate**

This section is adequate.

4. *Section 11 Description*

ALTRENO Lotion is an opaque, pale yellow lotion containing 0.05% tretinoin by weight for topical administration.

Chemically, tretinoin is all-trans-retinoic acid, also known as (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. It is a member of the retinoid class of compounds and a metabolite of vitamin A. Tretinoin has the following chemical structure:



Molecular Formula: $C_{20}H_{28}O_2$ Molecular Weight: 300.44

Each gram of ALTRENO Lotion contains 0.5 mg (0.05%) of tretinoin in an opaque, pale yellow lotion base consisting of benzyl alcohol, butylated hydroxytoluene, carbomer copolymer type B (Pemulen TR-1), carbomer homopolymer type A (Carbopol 981) glycerin, methylparaben, mineral oil, nitrogen, octoxynol-9, purified water, sodium hyaluronate, soluble collagen and trolamine.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	Altreno lotion	**should be revised to** Altreno (tretinoin) lotion **Not Adequate**
Dosage form and route of administration	lotion	**Adequate**
Active moiety expression of strength with equivalence statement (if applicable)	N/A	
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each gram of ALTRENO Lotion contains 0.5 mg (0.05%) of tretinoin in an opaque, pale yellow lotion base consisting of benzyl alcohol, butylated hydroxytoluene, carbomer copolymer type B (Pemulen TR-1), carbomer homopolymer type A (Carbopol 981), glycerin, methylparaben, mineral oil, (b)(4), octoxynol-9, purified water, sodium hyaluronate, soluble collagen and trolamine	**No need to include** (b)(4) **in the inactive ingredients** **Not Adequate**
Statement of being sterile (if applicable)	N/A	**Adequate**
Pharmacological/ therapeutic class	a member of the retinoid class of compounds and a metabolite of vitamin A	**Adequate**
Chemical name, structural formula, molecular weight	Provided	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Not provided	**The description section is similar to the approved Atralin gel** **Adequate**

This section is not adequate. The following revision should be made:

1) The Proprietary name and established name should be revised to Altreno (tretinoin) lotion in the beginning of the paragraph
2) No need to include (b)(4) in the inactive ingredients as it is (b) (4) (b) (4)

5. *Section 16 How Supplied/Storage and Handling*

ALTRENO (tretinoin) Lotion, 0.05% is an opaque, pale yellow topical lotion and available as:

- 45 g tube (NDC 0187-0005-45)

Storage and Handling Conditions

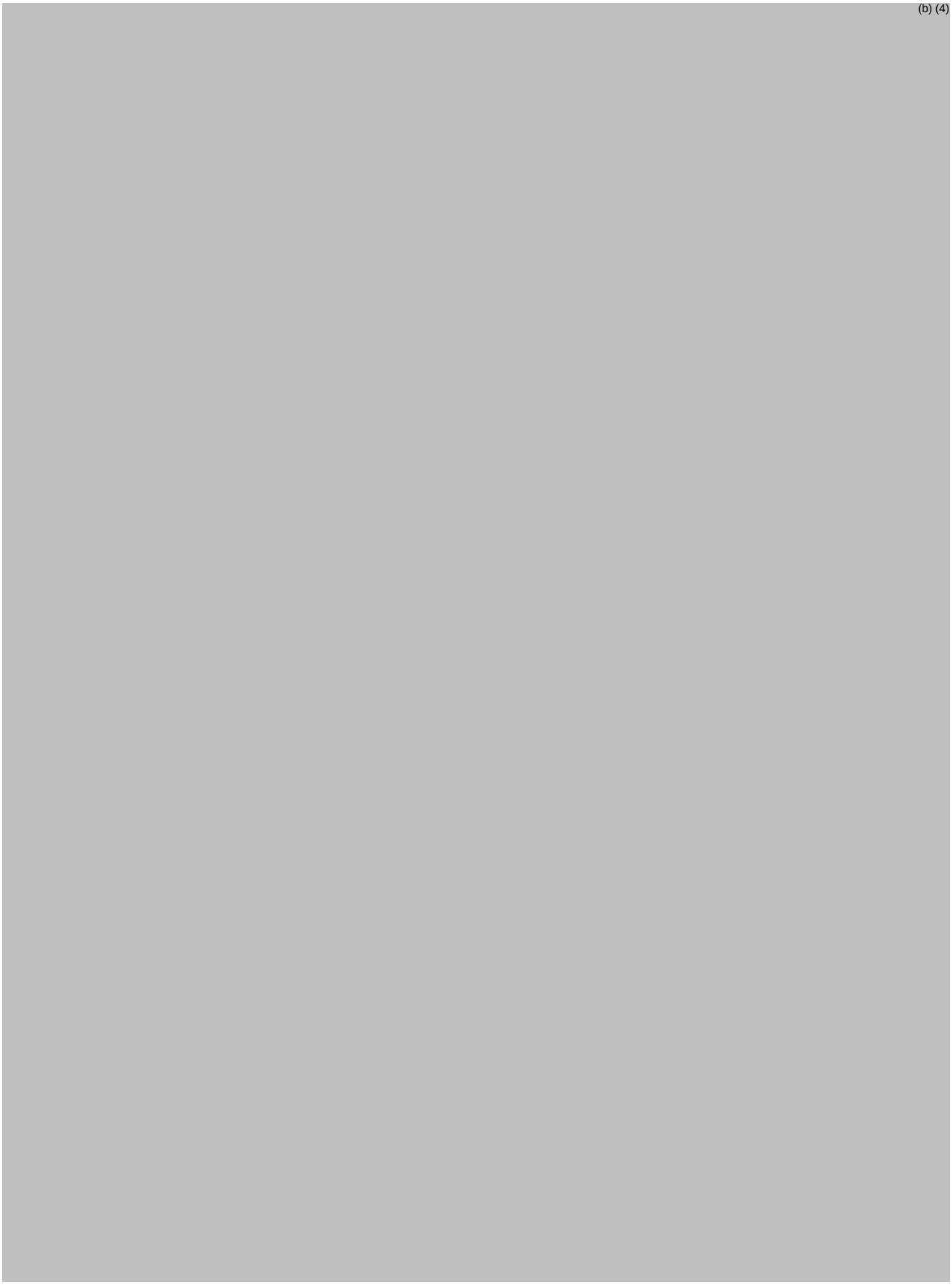
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	ALTRENO (tretinoin) Lotion, 0.05%	**Adequate**
Available units (e.g., bottles of 100 tablets)	45 g tube (NDC 0187-0005-45)	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	opaque, pale yellow topical lotion	**Adequate**
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	N/A	**Adequate**
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing	**Adequate**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	**Manufactured for:** Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Bridgewater, NJ 08807 USA **By:** Valeant Pharmaceuticals International, Inc. Laval, Quebec H7L 4A8, Canada Provided after section 17 Patient Counseling Information	**Adequate**

This section is adequate.

II. Labels:

1. **Immediate Container Label**


(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ALTRENO (tretinoin) Lotion	**Adequate**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	0.05%	**Adequate**
Net contents	45 g (3 g for physician sample)	**Adequate**
"Rx only" displayed prominently on the main panel	Provided	**Adequate**
NDC number (21 CFR 207.35(b)(3)(i))	Provided	**Adequate**
Lot number and expiration date (21 CFR 201.17)	it is indicated that "See crimp for lot number and expiration date."	**Adequate**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.	**Adequate**
Bar code (21CFR 201.25)	Provided	**Adequate**
Name of manufacturer/distributor	Provided	**Adequate**
And others, if space is available	**Each gram contains:** 0.5 mg (0.05%) of tretinoin in an opaque, pale yellow lotion base consisting of benzyl alcohol, butylated hydroxytoluene, carbomer copolymer type B (Pemulen TR-1), carbomer homopolymer type A (Carbopol 981), glycerin, methylparaben, mineral oil, (b)(4) octoxynol-	**No need to display (b)(4) in the inactive ingredients section** **Not Adequate**

This section is not adequate. The following revision should be made:

Delete (b)(4) in the inactive ingredient section

2. **Carton Label**

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	ALTRENO (tretinoin) Lotion	**Adequate**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	0.05%	**Adequate**
Net quantity of dosage form	45 g (6 tubes 3 g per tube for physician samples)	**Adequate**
"Rx only" displayed prominently on the main panel	Provided	**Adequate**
Lot number and expiration date	Provided	**Adequate**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.	**Adequate**
Bar code (21CFR 201.25)	Provided	**Adequate**
NDC number (21 CFR 207.35(b)(3)(i))	Provided	**Adequate**
Manufacturer/distributor's name	Provided	**Adequate**
Quantitative ingredient information (injectables)	**Each gram contains:** 0.5 mg (0.05%) of tretinoin in an opaque, pale yellow lotion base consisting of benzyl alcohol, butylated hydroxytoluene, carbomer copolymer type B (Pemulen TR-1), carbomer homopolymer type A (Carbopol 981), glycerin, methylparaben, mineral oil, (b)(4) octoxynol-9, purified water, sodium hyaluronate, soluble collagen and trolamine.	**No need to display (b)(4) in the inactive ingredients section** **Not Adequate**
Statement of being sterile (if applicable)	N/A	**Adequate**
"See package insert for dosage information"	**Usual Dosage:** Apply a thin layer to the affected area once daily. See package insert for complete prescribing information.	**Adequate**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Provided	**Adequate**

This section is not adequate. The following revision should be made:

Delete [redacted] in the inactive ingredient section

List of Deficiencies:

For the Labeling insert

Section 11 should be revised to:

1. The Proprietary name and established name should be revised to Altreno (tretinoin) lotion in the beginning of the paragraph
2. Delete [redacted] in the inactive ingredients as it is [redacted]

For the Container/Carton Labels:

1. Delete [redacted] in the inactive ingredients as it is [redacted]

Overall Assessment and Recommendation:

The labels and labeling are not acceptable for approval of this application until the above deficiencies are adequately addressed.

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Ge's assessment on the labels and labeling, and concur with her conclusion that this application is not ready for approval in its present form per 21 CFR314.125(b)(6) until the above deficiencies are resolved satisfactorily.

Moo-Jhong Rhee, Ph. D.
Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Date: 6/07/2018 11:28:37AM
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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
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CHAPTER V: Review of Biopharmaceutics

BIOPHARMACEUTICS

Product Background:

NDA: 209353 ORIG-1

Drug Product Name / Strength: ALTRENO ™ (tretinoin) Lotion, 0.05%

Route of Administration/indication: Topical treatment of acne vulgaris

Applicant Name: Dow Pharmaceutical Sciences (DPS)

The Applicant is seeking approval of ALTRENO™ Lotion 0.05% under NDA 209353. This submission follows the 505 (b)(1) path and thus, includes nonclinical and clinical data (e.g., PK data and two Phase 3 clinical trials) in support of the efficacy and safety of the proposed drug product to be administered once daily for the treatment of acne vulgaris. The submission also makes cross-reference to several NDAs for the same drug substance approved for several indications as supportive for long-term safety. The proposed drug product is a topical lotion containing the drug substance in (b) (4)

Review Summary:

The drug product under review is a lotion-based drug product (semisolid product) containing the drug substance (tretinoin) in (b)(4) indicated for the local treatment of acne vulgaris. According to the Applicant, the proposed drug product was designed with the same concentration of tretinoin in (b)(4) as the approved Atralin Gel, 0.05% formulation. As the drug is in (b) (4), particle size distributing is critical for the in vitro and in vivo performance of the drug product. Tretinoin (b) (4) and other inactive ingredient (b)(4) PSD. However, it was noted that the proposed specification for PSD was permissive and therefore, during the CMC filing meeting, it was suggested that the CMC recommend to the Applicant to revise the proposed PSD specifications (b) (4) On a submission dated 3/30/18, the Applicant provided a response (refer to CMC review for final assessment).

In accordance with current guidance recommendations[1] (i.e., the development and validation of an in vitro release test (IVRT) are not required for approval nor is the IVRT required as a routine batch-to-batch quality control test), the Applicant did not include IVRT as part of the drug product specifications table. Nevertheless, the Applicant was advised during the review cycle to "consider the development and validation of a robust and reproducible IVRT method (e.g. such as a Franz cell system) that is adequately sensitive to highlight the differences in physicochemical (e.g., particle size distribution) and rheological characteristics of your proposed drug product such as the composition, manufacturing process, and viscosity and stress conditions"…." Consider implementing IVRT acceptance criteria for your drug product as part

[1] Guidance for Industry- Nonsterile Semisolid Solid Dosage Forms
https://www.fda.gov/downloads/drugs/guidances/ucm070930.pdf

of drug product specifications (b) (4) (b)(4)

(b)(4)

The manufacturing site for the clinical and commercial product is Valeant Pharmaceuticals International, in Quebec, Canada. The assurance of the quality of the drug product relies on drug product specifications (other than in vitro release testing) and in process controls characteristic of topical lotion formulations.

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
10/27/18	0000
12/21/17	0004

Highlight Key Outstanding Issues from Last Cycle: NONE

Concise Description Outstanding Issues Remaining: NONE

From Biopharmaceutics perspective, NDA 209353 for* ALTRENO ™ (tretinoin) Lotion, 0.05% *is recommended for Approval.

Primary Biopharmaceutics Reviewer Name and Date:

Sandra Suarez Sharp, Ph.D. (Branch 2 DB\ONDP\OPQ), 6/07/18

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Vidula Kolhatkar, Ph.D., Acting Team Lead (Branch 2\DB\ONDP\OPQ), June 11, 2018

Vidula Kolhatkar

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Sandra Suarez

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Date: 6/14/2018 10:34:16AM
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CHAPTER VI: Review of Quality Microbiology

MICROBIOLOGY

Product Background:

NDA: 209353

Drug Product Name / Strength: ALTRENO™ (tretinoin) Lotion, 0.05%, multi-dose

Route of Administration: Topical

Applicant Name: Dow Pharmaceutical Sciences, Inc.

Manufacturing Site: Valeant Pharmaceuticals International, Inc.
2150 St. Elzear Boulevard West
Laval, Quebec, Canada H7L 4A8

Method of Sterilization: The drug product is non-sterile.

Review Recommendation: **Adequate**

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

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

Review Summary: See remarks.

List Submissions Being Reviewed: Seq 0001 (10/27/2017)- original submission; Seq 0003 (12/20/2017)-Response to CMC Information Request; Seq 0008 (04/02/2018)-Response to CMC Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The submission was provided in the eCTD format. The subject drug is a non-sterile, multi-dose lotion. A CMC information request was forwarded to the applicant by the Regulatory Business Process Manager on 16 March 2018. The applicant amended the application with responses to this information request on 02 April 2018. Applicant responses are summarized and reviewed in appropriate sections of this review. Overall, the submission is recommended for approval on the basis of product quality microbiology.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance- N/A.

Reviewer's Assessment: The drug substance manufacturing process is not the subject of this product quality microbiology review.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** –
(See Seq 0001, Section 3.2.P.1, *Description and Composition of the Drug Product.pdf*)

  The subject drug product is an opaque, pale, yellow, aqueous lotion for topical administration.

- **Drug product composition** –
(See Seq 0001, Section 3.2.P.1, *Description and Composition of the Drug Product.pdf)*

  Table 3.2.P.1-1 was provided for the finished product composition and reproduced below.

Table 3.2.P.1–1 Qualitative and quantitative composition of drug product

Component	Reference to Quality Standard	Function	Concentration (mg/g)	Concentration (% w/w)
Tretinoin	(b)(4)	Active	0.50[a]	(b) (4)
Glycerin			(b)(4)	(b)(4)
Methylparaben		Antimicrobial preservative		
Benzyl alcohol		Antimicrobial preservative		
Carbomer homopolymer type A (Carbopol 981)			(b)(4)	
Sodium hyaluronate				
Carbomer copolymer type B (Pemulen TR-1)				
Mineral oil				
Soluble collagen[b]				
Octoxynol 9				
Butylated hydroxytoluene				
Trolamine				
Purified water	(b)(4)			

a This ingredient is charged on the assay basis.
b This brand of soluble collagen contains (b)(4) (b)(4)

USP = United States Pharmacopeia
NF = National Formulary
qs = quantity sufficient

- **Description of container closure system** –
(See Seq 0001, Section 3.2.P.1, *Description and Composition of the Drug Product.pdf*)

The drug product is packaged as a nominal 3 g or 45 g fill size in a blind end aluminum tube with [redacted] and [redacted] cap.

Reviewer's Assessment: Adequate
The applicant provided an adequate description of the drug product composition and the container closure system.

P.2.5 Microbiological Attributes

- **Container/Closure and Package Integrity-** N/A. The drug product is non-sterile.

- **Antimicrobial Effectiveness Testing-**
(See Seq 0001, Section 3.2.P.2, *Microbiological Attributes.pdf*, pgs. 2-3)

[redacted]% Methylparaben and [redacted] Benzyl alcohol are included as preservatives in the formulation. The specification range for both Methylparaben and Benzyl alcohol is [redacted]% for release and for shelf life. Antimicrobial effectiveness testing (AET) per USP <51> was performed with drug product lots formulated with both preservatives a [redacted]%, and [redacted]% of the label claim. Method suitability testing was performed with modified Tryptic Soy Broth. Log reduction data for drug product lots formulated with both preservatives at all four concentrations were provided and met USP <51> acceptance criteria for Category 2 products. All challenge bacteria demonstrated [redacted] log reduction at 14 days and no increase at 28 days. All samples inoculated with *C. albicans* and *A. brasiliensis* demonstrated no increase at 14 and 28 days.

Reviewer's Assessment: Adequate
The applicant has met regulatory expectations for demonstrating the antimicrobial effectiveness requirement for a multiple dose drug product.

P.3 Manufacture
P.3.1 Manufacturers

Drug product manufacturing, release, and stability testing
Valeant Pharmaceuticals International, Inc.
2150 St. Elzear Boulevard West
Laval, Quebec, Canada H7L 4A8

[redacted]

Reviewer's Assessment: Adequate

P.3.3 Description of the Manufacturing Process and Process Controls-

- **Overall manufacturing operation**
  The subject drug product is a preserved, non-sterile, topical, dosage form. The manufacturing process consists of (b) (4) followed by filling into tubes with (b)(4)

Reviewer's Assessment: Adequate

- **Monitoring of BCC in the manufacturing process**
  (See Seq 0001, Section 3.2.P.3.2, *Microbiological Attributes.pdf,* pgs. 4-8)

  A risk assessment was conducted to identify potential sources for *Burkholderia cepacia* complex (BCC) introduction during the manufacturing process. The assessment examined raw materials and manufacturing areas that had the greatest potential to be sources of contamination. The outcome of the assessment led to the addition of BCC testing for raw materials (i.e., (b)(4)) and as part of the (b) (4) Also, the finished drug product will be tested for the absence of BCC at release.

Reviewer's Assessment: Adequate
The applicant's risk assessment and subsequent monitoring program for introduction of *Burkholderia cepacia* complex into the drug product are consistent with regulatory expectations for an aqueous, non-sterile, pharmaceutical product.

P.3.5 Process Validation and/or Evaluation- N/A. The subject drug product is a preserved, non-sterile, dosage form.

P.5 Control of Drug Product

P.5.1 Specifications

Microbial testing will be performed at release with the following criteria:

- Total Aerobic Microbial Count: NMT (b) (4)
- Total Combined Yeast/Mold Count: NMT (b)(4)
- Absence of *S. aureus* and *P. aeruginosa*
- Absence of *B. cepacia* complex

Assays of Methylparaben and Benzyl Alcohol will be performed at release with the criteria o (b) (4) % of target level (TL = (b)(4) for Methylpara enzyl alcohol, respectively).

P.5.3 Validation of Analytical Procedures

- **Microbial Limits**
  (See Seq 0001, Section 3.2.P.5.3, *Validation of Microbial Testing-USP.pdf* and *Validation of Microbial Testing-B. cepacia Complex.pdf*)

Method suitability testing was performed for microbial enumeration per USP <61> and specified microorganisms (i.e., *S. aureus* and *P. aeruginosa*) per USP <62> with acceptable results.

A summary of the method validation study for the routine evaluation for the absence of *B. cepacia* was provided. Validation was performed with the following strains: (b)(4). These strain (b)(4)

(b)(4)

16 March 2018 Information Request:
It is acknowledged tha (b) (4) is proposed as an alternate microbiological testing facility. However, it is unclear if the same validated/verified methods that were provided for the Valeant Pharmaceuticals International, Inc. facility to examine microbial limits (i.e., microbial enumeration per USP <61>, absence of specified microorganisms per USP <62>, and absence of Burkholderia cepacia complex per reference method (b)(4) of the drug product for release and as part of the stability program will be used a (b) (4) Therefore, confirm that the same methods will be used at the two facilities. If not, provide a description of the alternative methods and verification of the methods suitability for finished product testing a (b) (4)

Summary of the applicant's response, dated 02 April 2018 (b)(4) will employ the same validated/verified microbiological test methods that were provided for the Valeant Pharmaceuticals International, Inc. facility.

Reviewer's Assessment: Adequate

The applicant has met regulatory expectations for validating/verifying the methods that are used to confirm the finished drug product meets the acceptance criteria for microbial limits.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(See Seq 0001, Section 3.2.P.8.1, *Stability Summary and Conclusions.pdf*)

A 24 month expiry has been proposed for the subject drug product.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(See Seq 0001, Section 3.2.P.8.2, *Post-approval Stability Protocol and Stability Commitment.pdf*)

Microbial limits testing is not proposed as part of the post-approval stability protocol. AET will be performed at the proposed expiry for three validation lots. However, AET (b)(4) The applicant states that (b)(4) (b)(4)"

One lot of each fill size will be placed on the stability program annually.

P.8.3 Stability Data

(See Seq 0001, Section 3.2.P.8.3, *Stability Data-25C.pdf, Stability Data-30C.pdf,* and *Stability Data-40C.pdf*)

Stability data for three bulk lots (#s 8087748, 8086695, and 8086696) were provided. The lots were (b) (4) into 3 g and 45 g fills, placed on stability in either the (b) (4) (b) (4) positions, and stored at 25°C/60%RH, 30°C/65%RH, and 40°C/75%RH. AET was performed at initial and 6 months for samples stored at 40°C/75%RH and at initial and 12 months for samples stored at 25°C/60%RH and 30°C/65%RH. Samples at all conditions and time points passed AET.

16 March 2018 Information Request:

The post-approval stability protocol provided in Section 3.2.P.8.2 is acknowledged. However, the protocol does not include a test for microbial enumeration through the proposed shelf life. ICH Q1A(R2): Stability Testing of New Drug Substances and Products (2003) states that "stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system)." Therefore, modify the proposed post-approval stability protocol to include periodic testing of microbial enumeration per USP <61> with acceptance criteria per USP <1111>.

Summary of the applicant's response, dated 02 April 2018: The post-approval stability protocol has been updated to include microbiological testing (i.e., TAMC; TYMC; absence of *S. aureus*, *P. aeruginosa*, and BCC) to be performed annually.

Reviewer's Assessment: Adequate
The ATL and Drug Product reviewers indicated that firms do not typically follow ICH guidelines for microbial limits testing frequency. Firms normally perform testing annually to the expiry. Therefore, the proposed frequency for testing is deemed acceptable.

Additionally, the applicant does not commit to placing the first three commercial production batches on stability. However, data from stability studies were provided for three ICH registration stability lots (#s 8086695, 8086696, and 8087448) that are being stored under the same conditions (25°±2°C/60±5%RH) as are proposed for the stability protocol for commercial production. The registration lots were manufactured at the commercial production scale of (b)(4) kg, which were then (b) (4) into 3 g and 45 g fill sizes. The lots were prepared with drug substance from (b)(4) (b)(4) using the proposed manufacturing process at the proposed commercial manufacturing facility (b) (4) The applicant states that "the stability study for these lots is ongoing and the additional data will be provided in future submissions to this market application." Per *ICH Q1A(R2): Stability Testing of New Drug Substance and Products*, as the submission includes data from stability studies on at least three production lots and there is a commitment to continue these studies through the proposed re-test period, a post approval commitment to place the first three commercial production batches on stability is unnecessary. Therefore, this commitment will not be requested from the applicant.

Overall, the applicant has met regulatory expectations with regard to the design of the post-approval stability testing program to support the drug product's microbiological quality throughout its shelf life.

R Regional Information
Executed Batch Records- N/A.

Comparability Protocols- N/A.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1
2.A. Package Insert- N/A.

Post-Approval Commitments- N/A.

Primary Microbiology Reviewer Name and Date: Daniel J. Schu, Ph.D., 17 May 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
John W. Metcalfe, Ph.D. I concur with the primary reviewer's assessment. 17 May 2018

Daniel Schu

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John Metcalfe

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Comments: I concur with the primary reviewer's assessment.

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