

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208552Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: January 18, 2017
From: Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 208552

Subject: Final Approval Recommendation for NDA 208552

At the time when the CMC review #1 was written, resolution of issues on Labels and Labeling was pending.

Additionally, on January 3, 2017, an IR letter requesting the NDA applicant to address cGMP related deficiencies identified by the facility reviewer, Dr. Bleta Vuniqui, from the Office of Compliance of CDRH, was sent. The applicant provided an amendment responding to the IR letter on January 6, 2017.

Update of the Status of Facility Inspection

Dr. Bleta Vuniqui, who is the facility reviewer from the Office of Compliance at CDRH (The Center for Devices and Radiological Health) for the NDA, has reviewed the response to the IR letter. She recommended approval of the facilities used for manufacturing and test of the airless pumps (which are deemed to be devices according to CDRH recommendation) of the NDA from CDRH's perspective on January 9, 2017. Her review is attached below (**Attachment - 1**).

Label/Labeling

On January 3, 2017, the NDA applicant provided the finalized mock up container and carton labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert on January 17, 2017. All the labels/labeling issues are now satisfactorily resolved. The review of the CMC sections of the final package insert, and mock up container and carton labels was conducted by Dr. Hong Cai, and is attached below (**Attachment - 2**).

Recommendation:

The revised package insert, and mock-up container and carton labels are now satisfactory from the CMC perspective. Additionally, deficiencies related to cGMP of the pump manufacturing and testing sites have been satisfactorily resolved. Therefore, from the OPQ's perspective, this NDA is recommended for **APPROVAL** with an expiration dating period of **18** months granted for the drug product.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from a quality perspective.

Yichun Sun, Ph.D.

Application Technical Lead, Branch V

Division of New Drug Products II

1/18/2017

Attachment – 1: CDRH Consult Review on Facilities

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality

Date: December 29, 2016
Updated: 01/09/2017

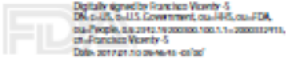
To: Cai Hong, Chemist, CDER/OPQ/ONDP/DNDPII/NDPBV. WO 21 RM2605
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Rhee, Moo Jhong, Supervisory
Chemist, CDER/OPQ/ONDP/DNDPII/NDPBV. WO22 RM1462
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Office of combination products at combination@fda.gov

Through: Vicenty Francisco, Chief, REGO, DMQ, OC, CDRH

**Francisco
Vicenty -S**



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From: Blea Vuniqui, DMQ, OC, CDRH

Applicant: Allergan Inc.
2525 Dupont Drive, P.O. Box 19534
Irvine, CA, 92623
(b) (4)

Application # NDA 208552

Consult # ICC# 1600496

Product Name: Rhofade Crem

Combination Product

Intended Use: The product is intended to treat persistent facial erythema associated with rosacea.

Pre-Approval Inspection: No

Documentation Review: No Additional Information Required

Final Recommendation: Approval

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 208552.

PRODUCT DESCRIPTION

The product is intended to treat persistent facial erythema associated with rosacea. The finished product will be packaged for commercial distribution in any of these three primary container closure systems:

1. Laminate tubes with child-resistant closures (CRC). The tubes come in two sizes: 30 mL and 60 mL, and consist of HDPE (b) (4) with an aluminum foil laminate tube structure.
2. Airless pump containers with CRC. The airless pump container consists of a polypropylene bottle with (b) (4) and HDPE (b) (4). Other components of the pump container include a child-resistant cap, actuator, (b) (4). (b) (4). The pump bottles come in two sizes: 30 mL and 60 mL.
3. The 3 mL professional sample will be packaged in a laminate tube with CRC.

REGULATORY HISTORY

The information provided by the applicant is unclear. It is unknown which facilities are subject to applicable Quality System Requirements under 21 CFR part 820.

Updated 01/09/2017:

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

- (b) (4)

Responsibility – (b) (4) responsible for the ensuring the the non-metered airless pump for Oxymetazoline cream, 30g and 60g is manufactured per the defined specifications; therefore the facility is subject to 21 CFR 820 QS requirements.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted on (b) (4). The inspection covered medical device QS requirements and was classified NAI. An inspection is not required because a recent inspection of the firm was acceptable.

- (b) (4)

Responsibility – The facility responsible for manufacturing the non-metered airless pump for Oxymetazoline cream, 30g and 60g; therefore the facility is subject to 21 CFR 820 QS requirements.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. FACTS shows that the firm is not workload obligation. The device is a low risk device and the applicant is responsible for ensuring the manufacturing is controlled through supplier controls. The applicant was inspected and no observations were identified; therefore an inspection is not required.

- DPT Laboratories, Ltd
307 E Josephine Street
San Antonio, TX 78215
FEI#: 1628114

Responsibility – The facility responsible for manufacturing the drug product, (b) (4); therefore the facility is subject to 21 CFR 820 QS requirements.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted on 08/15-23/2016. The inspection covered drug GMP and medical device QS requirements and was classified NAI. An inspection is not required because a recent inspection of the firm was acceptable.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product, and the firm did not provide information to fulfill these requirements.

Management Control, 21 CFR 820.20

The information provided by the firm did not address the requirements of 21 CFR 820.20.

Updated 01/09/2017:

The firm provided the Quality Management Structure. They further described the organizational structure and management review process.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The information provided by the firm did not address the requirements of 21 CFR 820.30.

Updated 01/09/2017:

The firm provided a description of their design control and their process. The firm also described how the design is controlled through the contract facilities and suppliers.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The information provided by the firm did not address the requirements of 21 CFR 820.50.

Updated 01/09/2017:

The applicant described their process for supplier selection and evaluation. The applicant described the process how the suppliers are evaluated and reviewed on their ability to meet quality requirements.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The information provided by the firm did not address the requirements of 21 CFR 820.100.

Updated 01/09/2017:

The firm described their CAPA process and how the CAPA system is integrated with the different sites.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

The firm provided a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review.

Figure 1 Process Flow Diagram for Production Scale Manufacture of Oxymetazoline HCl Cream, 1.0%



Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The application for Rhofade Crem – NDA 208552 is approvable from the perspective of the applicable Quality System Requirements.

Bleta Vuniqui
 -S

 Bleta Vuniqui

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Prepared: BVuniqui: 12/29/2016
Reviewed: FVicenty: 12/30/2016
Revised: BVuniqui: 01/09/2017
Reviewed: FVicenty: 01/09/2017

CTS No.: ICC1600496
Application Number: NDA 208552

Attachment – 2: Review of CMC Sections of the Finalized Package Insert, and Container and Carton Labels

Memorandum

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

Date: January 13, 2017

From: Hong Cai, Ph.D.
Drug Product Reviewer,
Branch V Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 208552

Subject: Finalized Label/labeling of CMC Sections

At the time when Labeling Review of this application was completed (12/07/2016), this NDA was not recommended for approval due to unresolved CMC label/labeling issues. To resolve the outstanding label/labeling issues, the applicant submitted the amendments to the NDA on 01/03/2017 and 01/17/2017 that provide the revised package insert (PI), and container and carton labels. The revised labels/labeling adequately addressed all CMC labeling issues (see the **Attachment-1** and **Attachment-2**).

(b) (4)

those have been reviewed and accepted by DMEPA reviewer Carlos Mena-Grillasca according to the email correspondences to OND RPM Dawn Williams on January 5 and 12, 2017.

Recommendation:

The outstanding CMC label/labeling issues have been resolved. This application is now recommended for approval from the labeling perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP



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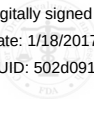
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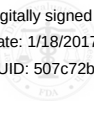
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Yichun
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Recommendation:

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 208552
Review # 1

Drug Name/Dosage Form	RHOFADE (Oxymetazoline Hydrochloride) Cream
Strength	1.0%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Allergan Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	03-23-2016	All
Amendment	06-28-2016	Biopharmaceutics and drug product
Amendment	07-18-2016	Drug product (pump)
Amendment	07-22-2016	Biopharmaceutics and drug product
Amendment	08-02-2016	Drug product (pump)
Amendment	08-18-2016	Biopharmaceutics
Amendment	09-26-2016	Drug product
Amendment	10-28-2016	Drug product
Amendment	11-07-2016	Drug product (labeling)
Amendment	11-17-2016	Drug product (labeling)
Amendment	11-30-2016	Facility and drug product
Amendment	12/07/2016	Drug product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeff Medwid	Branch II/Division of New Drug API
Drug Product	Hong Cai	Branch V/Division of New Drug Products II
Process	Yaodong Huang	Branch VIII/Division of Process Assessment III
Microbiology	Julie Nemecek	Branch III/Division of Microbiology Assessment
Facility	Brian Ryan	Branch III/Division of

		Inspection Assessment
Biopharmaceutics	Kelly Kitchens	Branch II/Division of Biopharmaceutics
Regulatory Business Process Manager	Grafton Adams	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
CDRH Senior Regulatory Research Reviewer	Keith Marin	General Hospital Devices Branch/Division of Anesthesiology, General Hospital, Infection Control, & Dental Devices/Office of Device Evaluation/CDRH
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)	(b) (4)	3	November 23, 2015	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			1	8/10/2016	Approval

Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

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
EOP2 Meeting Minutes	107983	Discussions of the clinical development plan for the IND.
Pre-NDA Meeting Minutes	107983	Discussion of the content and format of the proposed NDA submission for Rhofade cream.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----	N/A	----	----
Pharmacology/Toxicology	----	N/A	----	----
CDRH	Complete	Approval	8/10/2016	Keith Marin
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 “Approval” recommendation for the facilities involved in this application.

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

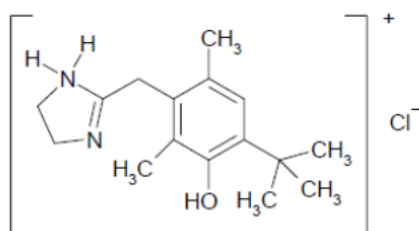
Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved (See the List of Deficiencies on pp. 9-10).

II. Summary of Quality Assessments

A. Product Overview

Drug Substance

The active ingredient used in Rhofade cream, 1% is oxymetazoline hydrochloride, which is highly selective for the α_1A adrenoceptor over other α_1 adrenoceptors and nonselective for the α_2 adrenoceptors. Oxymetazoline hydrochloride has a chemical name of 3-[(4,5-Dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethyl-phenol hydrochloride and a molecular weight of 296.8. The molecular formula of oxymetazoline hydrochloride is $C_{16}H_{25}ClN_2O$ and its structural formula is:



Detailed CMC information on oxymetazoline hydrochloride is provided in DMF # (b) (4) referenced. DMF # (b) (4) has been reviewed and found adequate in supporting the use of the drug substance in the drug product of this NDA.

Drug Product

The drug product is Rhofade (oxymetazoline hydrochloride) cream, 1%. Oxymetazoline hydrochloride cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults. It is a white to off-

white cream available in tubes and pump bottles. Each gram of the cream contains 10 mg (1.0%) oxymetazoline hydrochloride. The cream contains the following inactive ingredients: sodium citrate dihydrate, citric acid anhydrous, disodium edetate dihydrate, butylated hydroxytoluene, anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol 300, PEG-6 stearate, glycol stearate, PEG-32 stearate, cetostearyl alcohol, cetareth-6, stearyl alcohol, cetareth-25, methylparaben, propylparaben, phenoxyethanol, and purified water. The cream is prepared by (b) (4)



In-process controls and tests implemented during the manufacturing process of the cream are:

 (b) (4)

The cream is packaged in the following packaging configurations:

- Laminate tubes with child-resistant closures (CRC). The tubes come in two sizes: 30 mL and 60 mL.
- Airless pump containers with CRC. The pump bottles come in two sizes: 30 mL and 60 mL.
- The 3 mL professional samples will be packaged in a laminate tube with CRC.

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. An in vitro release test (IVRT) of the cream has been developed. The facility review team from the Office of Process and Facilities (OPF) has provided an Overall Acceptable recommendation for the facilities involved in the manufacture and test of the drug substance and drug product. The expiration dating period of **18** months is recommended for the drug product when stored at controlled room temperature

based on long-term and accelerated stability data obtained from primary registration batches of the drug product, and supportive stability data. The NDA applicant's request for a categorical exclusion from an Environmental Assessment (EA) is deemed acceptable. The indication and recommended daily dose of the drug product are summarized in the following Table.

Proposed Indication(s) including Intended Patient Population	Oxymetazoline cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.
Duration of Treatment	N/A
Maximum Daily Dose	Apply a pea-sized amount once daily in a thin layer to cover the entire face.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The active ingredient used in Rhofade cream 1.0% is oxymetazoline hydrochloride. Detailed CMC information on oxymetazoline hydrochloride is referred to DMF # (b) (4). DMF # (b) (4) has been reviewed and found adequate in supporting the use of the drug substance in the drug product of this NDA. The review on the CMC information of the drug substance has been conducted by Dr. Jeffrey Medwid. His review is attached (**CHAPTER I: Review of Drug Substance**).

Drug Product

The drug product of the NDA is Rhofade (oxymetazoline hydrochloride) cream 1%. Rhofade contains 1% (w/w) oxymetazoline hydrochloride, equivalent to 0.88% (w/w) of oxymetazoline. The drug product contains the following excipients: anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol 300, (b) (4), cetostearyl alcohol, butylated hydroxytoluene, disodium edetate dihydrate, sodium citrate dihydrate, citric acid anhydrous, phenoxyethanol, propylparaben, methylparaben and water. All the excipients are compendial grades with the exception for diisopropyl adipate, (b) (4). The quality of the non-compendial excipients is deemed adequate to support this application based on the material information and COAs, and the in-house release specifications proposed by the NDA applicant. The packaging configurations of Rhofade for commercial supplies are: 30mL/30g and 60mL/60g tubes; 30mL/30g and 60mL/60g non-metered pumps. Additionally, a 3mL/3g tube configuration is provided for professional samples. All container closure configurations come with the child-resistant closures (CRC). The tube configurations are deemed adequate to the patient safety and formulation

protection. Rhofade cream in non-metered dose pump is considered a drug-device combination product. The adequacy of the design, function and safety of the pump device including the referred DMF (# (b) (4)) has been reviewed by a CDRH reviewer, Lieutenant Commander, Keith Marin. He recommended an approval for this combination product. His review is attached (**CHAPTER VIII: CDRH Consult Review on the Non-metered Dose Pump**).

Specification for Rhofade cream is adequate to ensure the identity, strength, purity, and quality of the drug product and the quality of the to-be marketed drug product to be consistent with pivotal clinical batches of the drug product. Two drug product manufacture sites were proposed to produce the to-be marketed Rhofade cream, namely DPT and (b) (4). Stability data of five batches from DPT labs support an expiration dating period of 18 months when stored at (b) (4) RH with excursions permitted to 15°C to 30°C (59°F to 86°F). 6 months of the stability data from the three batches of (b) (4)



A claim for categorical exclusion from the environmental assessment was granted. Rhofade (oxymetazoline hydrochloride) cream, 1% is recommended for **approval** from the Drug Product perspective. The review on the CMC information of the drug product has been conducted by Dr. Hong Cai. Her review is attached (**CHAPTER II: Review of Drug Product**).

***Note:** The applicant withdrew (b) (4) manufacturing facility from the NDA on November 30, 2016 due to cGMP violations on the site. DPT Laboratories, Ltd., San Antonio-TX, will be used to manufacture the drug product. Although the data related to the drug product batches manufactured at (b) (4) site including batch release and stability have been reviewed, those data are not used to support the approval this NDA.

Labeling and Labels

The Sections of the Package Insert related to CMC, and container and carton labels of the NDA have been reviewed:

Package Insert

The following sections of the package insert have been reviewed.

1. Names and Dosage Forms and Strengths in the Highlights of Prescribing Information

2. Sections 3 (Dosage Forms and Strengths), #11 (Description) and #16 (How Supplied/Storage and Handling) in the Full Prescribing Information

Container and Carton Labels

Container and carton labels of tube and pump packaging configurations have been reviewed.

Issues Remained to be Resolved:

I. Package Insert

A. Highlight Section

1. The established name of the drug substance should be revised. The drug title should read as “Rhofade (oxymetazoline hydrochloride) cream, for topical use only”. Please revise the established name of the drug substance throughout the Package Insert (PI). HCl should be spelled out throughout the PI.
2. Dosage Form and Strengths:
Revise the dosage form and strength to read as “Cream, 1%”. Revise the dosage form to “Cream” throughout the PI document.
Revise strength expression to “each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8mg (0.88%) of oxymetazoline free base”

B. Full Prescribing Information

#3 Dosage Form and Strengths:

1. This Section should be revised to read as “RHOFADETM (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. Each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8mg (0.88%) of oxymetazoline free base.”

#11 Description:

1. The established name of the drug substance in the drug title should be revised to “oxymetazoline hydrochloride”. The drug title should read as “Rhofade (oxymetazoline hydrochloride) cream”.
2. The following inactive ingredients should be revised to reflect the excipients used: “(b) (4)” to “sodium citrate dihydrate”; “(b) (4)” to “citric acid anhydrous”; “(b) (4)” to “disodium edetate dihydrate”.

3. Provide important chemical or physical properties for the drug substance, oxymetaxoline hydrochloride.
4. Oxymetazoline hydrochloride pharmacological class needs to be revised according to the clinical recommendation. Revise it to be as “RHOFADE (oxymetazoline hydrochloride) cream, 1% contains oxymetazoline hydrochloride, an alpha1A adrenoceptor agonist.”
5. Correct the expression for Cl. (Cl is not (b)(4))

#16 How Supplied/Storage and Handling:

- The established name is not correct. Revise to “RHOFADE™ (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. The product is available in tubes and pump bottles and is supplied in the following packaging configurations, each with a child-resistant closure”.

II. Container/Carton Label

1. Revise the drug product title and its strength to the following:
Rhofade (oxymetazoline hydrochloride) cream, 1%

In addition, the strength equivalency statement based on the active moiety, oxymetazoline, should also be included in the label.
2. The name of following inactive ingredients should be revised to reflect the excipients actually used:
“(b)(4)” should be revised to “sodium citrate dihydrate”;
“(b)(4)” should be revised to “citric acid anhydrous”; “(b)(4)”
“(b)(4)” should be revised to “disodium edetate dihydrate”.
3. Ensure the presentation of the established name of the drug on all panels is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
4. Revise the dosage form from “(b)(4)” to “cream”.
5. For pump packaging configuration, the following information should be included: “Important: Prime pump before initial use and discard the product from the first three pumps.”

The review of the Package Insert and container and carton labels has been conducted by Dr. Hong Cai. Her review is attached (**CHAPTER III: Review of Labeling and Labels**)

Drug Product Manufacturing Process

The manufacturing process for oxymetazoline hydrochloride cream, 1% includes

(b) (4)

[REDACTED]

In-process controls and tests implemented during the manufacturing process of the cream are:

(b) (4)

[REDACTED]

The manufacturing process is adequately developed. In-process tests and controls are deemed acceptable. The drug product with satisfactory quality attributes can be produced using the drug product manufacturing process. Additionally, no scale-up issues for commercial production of the drug product are anticipated. 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. Yaodong (Tony) Huang. His review is attached (**CHAPTER IV: Review of Drug Product Manufacturing Process**).

Biopharmaceutics

The pilot scale (b) (4) batches of the drug product were used in Phase 3 clinical trials and registration stability studies. The batch size of the commercial production will be (b) (4). The Applicant plans to add (b) (4) as an alternate commercial manufacturing site by demonstrating its equivalence with the primary site, DPT Laboratories (San Antonio, TX). The following assessments were evaluated to support (b) (4) as an alternate manufacturing site:

(b) (4)

[REDACTED]

(b) (4)

(b) (4)

From the Biopharmaceutics perspective, NDA 208552 for Rhofade (oxymetazoline hydrochloride) cream, 1% is **acceptable**. The review on the biopharmaceutics of the drug product of the NDA has been conducted by Dr. Kelly Kitchens. Her review is attached (**CHAPTER V: Review of Biopharmaceutics**).

***Note:** The applicant withdrew (b) (4) manufacturing facility from the NDA on November 30, 2016 due to cGMP violations on the site. DPT Laboratories, Ltd., San Antonio-TX, will be used to manufacture the drug product. Although the data related to the drug product batches manufactured at (b) (4) site including batch release and stability have been reviewed, those data are not used to support the approval this NDA.

Quality Microbiology

(b) (4)

Antimicrobial Effectiveness Testing (AET) was performed per USP <51> with samples at 50%, 80%, and 100% of the target concentrations for the (b) (4). The specifications for microbial enumeration and the absence of *E. coli* and *P. aeruginosa* are consistent with those suggested in USP <111> for a topical product. The applicant describes adequate controls to detect potential contamination with *B. cepacia* (*Burkholderia cepacia* complex (BCC)). 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. Julie Nemecek. Her review is attached (**CHAPTER VI: Review of Quality Microbiology**).

Facilities

The manufacturing site of the active ingredient (oxymetazoline hydrochloride) in the drug product of this NDA is (b) (4) (FEI Number: (b) (4)) located in (b) (4). Based on the experience with non-sterile chemically synthesized manufacturing, the monographed history of the proposed API, the previous inspection history, and the firm's ability to correct deficiencies and implement adequate preventive measures, the facility is considered **acceptable** to manufacture the oxymetazoline hydrochloride drug substance in support of the NDA.

The applicant has proposed two finished drug product manufacturing sites for oxymetazoline hydrochloride cream, 1.0%, namely, (b) (4) and DPT Laboratories (FEI Number: 1628114) located in San Antonio, TX. The applicant also proposes the use of three contract testing labs (b) (4) (FEI number: (b) (4)); (b) (4) (FEI Number: (b) (4)) and Allergan Pharmaceuticals Ireland (FEI Number: 3002806285)] to support release and stability testing of the drug product.

The drug product manufacturing site, DPT Laboratories (FEI Number: 1628114) located in San Antonio, TX is deemed acceptable to perform the manufacturing operations of the oxymetazoline hydrochloride cream, 1%. The three contract testing labs (b) (4) (FEI number: (b) (4)); (b) (4) (FEI Number: (b) (4)) and Allergan Pharmaceuticals Ireland (FEI Number: 3002806285)] are also deemed acceptable to perform the proposed release and stability testing of the oxymetazoline hydrochloride cream, 1%.

However, the current inspectional status of (b) (4) prohibits it from supporting the drug product manufacturing for the current NDA. The firm has shown inability to correct previously identified manufacturing issues as shown from repeat 483 observations and particulate matter concerns discovered in the recent inspection. Currently, OPF does not have a high degree of confidence in the (b) (4) site that can reliably and reproducibly manufacture the drug product meeting the quality requirements over the product lifecycle. Thus, this facility is considered **unacceptable** to manufacture oxymetazoline hydrochloride cream, 1% in support of NDA 208552.

On November 30, 2016, the applicant submitted an amendment to the NDA to withdraw this facility as an alternate drug product manufacturing site. Based on the applicant's withdrawal of the current pOAI site, the commitment not to manufacture commercial product at this alternate site until the concerns identified in the recent inspection are adequately addressed, and the commitment to re-submit the facility for approval, OPF/DIA considered this facility withdrawn. The (b) (4) facility's compliance status will not affect the overall approvability of the NDA. All the current active facilities are deemed **acceptable** in their identified functions and responsibilities to support approval of NDA 208552. The facility review of the NDA has been conducted by Consumer Safety Officer, Brian Ryan. His review is attached (**CHAPTER VII: Review of Facilities**).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies for Complete Response (Attachment II)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Risk Assessment for NDA 208552 [Rhofade (oxymetazoline hydrochloride) Cream, 1%]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay (Oxymetazoline HCl)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	1	12	The content of the drug substance in the drug product is monitored using an HPLC method. Assay is one of the testing parameters in the drug product release and stability studies. It is measured by a validated HPLC/UV method. The registration stability batches demonstrated that the assay values remained within the specification acceptance criterion under the long term storage condition for 12 months without trending. Additionally (b) (4) BHT, (b) (4) (b) (4) is also monitored using a validated HPLC method at batch release and during stability studies.
Oxymetazoline Related Substances (b) (4) Individual unspecified, unknown and Total impurities)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	1	12	The levels of related impurities (b) (4) are controlled in the drug product at batch release and during stability studies. They are determined by a validated HPLC/UV method. They have been closely monitored during stability study with trending analysis.

(b) (4) (Phenoxyethanol Methylparaben Propylparaben)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	1	9	Phenoxyethanol, methylparaben and propylparaben are used as preservatives in the drug product. The levels (b) (4) in the drug product are monitored using a validated HPLC/UV method at release and during stability studies. The contents (b) (4) (b) (4) are controlled according to the acceptance criteria set in the drug product specification. The levels (b) (4) (b) (4) in the registration batches of the drug product were within the specification limits at release and during stability studies.
Microbial Limits (Total Yeasts and Molds Count, Total Aerobic Microbial Count, and Absence of Staphylococcus aureus, Pseudomonas aeruginosa, Burkholderia cepacia)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	1	12	(b) (4) validated HPLC/UV method at batch release and during stability studies. Microbial limit tests are included in the drug product specification. The results of microbial limit tests were within the specification limits at release and during stability studies.

pH	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	2	18	pH is one of the testing parameters included in the drug product batch release and stability testing. The pH values of the clinical and the registration stability batches of the drug product were within the specification acceptance criterion.
Apparent Viscosity (cps)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	2	18	(b) (4) (b) (4) The results of viscosity test for the registration batches of the drug product were within the specification acceptance criterion.
Within Container Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	4	4	1	16	(b) (4) (b) (4) The data in NDA demonstrated that the within container uniformity of the registration batches of the drug product met the acceptance criteria of specification, which conform to USP <3>.

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- $RPN \leq 25$

Moderate Risk - $25 < RPN \leq 60$

High Risk - $RPN > 60$

ATTACHMENT II: List of Deficiencies for Complete Response

A. Drug Substance Deficiencies: None

B. Drug Product Deficiencies: None

C. Environmental Analysis Deficiencies: None

D. Labeling Deficiencies: None.

E. Process Deficiencies: None

F. Facilities Deficiencies: None

G. Biopharmaceutics Deficiencies: None

H. Microbiology Deficiencies: None

OVERALL ASSESSMENT AND SIGNATURES:**Application Technical Lead's Assessment and Signature**

From quality 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
12/13/2016

Yichun
Sun -S

Digitally signed by Yichun Sun
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Yichun Sun -S,
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CHAPTERS: Primary Quality Assessment

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Hong Cai, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

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

I agree with Dr. Cai's assessment on the overall control strategy for the product including raw material controls, specification, container closure system, and stability of the product with 18-month of expiration dating period. Therefore, I concur with her recommendation of approval for this application from the drug product perspective.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

Cai, Hong

From: Laurenson, James
Sent: Monday, May 02, 2016 2:09 PM
To: Cai, Hong
Subject: RE: EA Review Consultation (NDA 208552)
Attachments: OPQ IQA Review Guide (v2) 18FEB2016.pdf

Hi Hong, we have guidance now in the IQA review guide, p. 27, attached. The sponsor doesn't have to provide a calculation (though I think they should!), so if you think it might be close to (b) (4) of use across all uses, which means it's for drugs with a large patient population), then you should look into it more (e.g., calculate a rough estimate of quantity based on patient population and dosing) or ask them for the calculations. Existing use from IMS data is also helpful. In this case, the API is currently at about (b) (4). I'm looking into whether we can give chemists access to our IMS data.
Jim

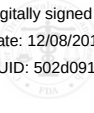
From: Cai, Hong
Sent: Monday, May 02, 2016 9:15 AM
To: Laurenson, James
Subject: EA Review Consultation (NDA 208552)

Jim,
Please advance how to proceed with NDA 208552 EA claim, the applicant claim "a categorical exclusion from the requirement to prepare an Environmental Assessment for Oxymetazoline HCl, 1% in accordance with 21 CFR 25.31 (b).", but no detailed calculations provided. Please refer to 1.12.14 for details in the application.
The OPQ kick off meeting is tomorrow and OND filing meeting is next week. Thanks.
Best regards,
Hong



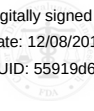
Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 12/08/2016 09:52 23AM
GUID: 502d0913000029f9798ca689a802fa55



Hong
Cai

Digitally signed by Hong Cai
Date: 12/08/2016 09:40 32AM
GUID: 55919d6500e16bdaad5825645e4f22ff



CHAPTER III: Review of Labeling and Labels

LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RHOFADETM topical cream safely and effectively. See full prescribing information for RHOFADETM topical cream.

RHOFADE™ (oxymetazoline) topical cream

For topical use (b) (4)

Initial U.S. Approval: 1964

-----DOSAGE FORMS AND STRENGTHS-----



QUALITY ASSESSMENT



Cream, (b) (4) Each gram of cream contains 10 mg (1%) oxymetazoline HCl, equivalent to 8.8mg (0.88%) of oxymetazoline free base (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name: Rhofade™ (b) (4) cream Established Name: (b) (4) cream	Not Satisfactory. The established name is not presented correctly. See detailed comments in Reviewer's Assessment. HCl should be spelled out throughout the PI document. Revise to "Rhofade (oxymetazoline hydrochloride) cream, For topical use only"
Dosage form, route of administration	RHOFADE™ (b) (4) cream For topical use only	Not Satisfactory. Per Product Title Guidance (2012), (b) (4) needs to be removed from the cream dosage form. Revise to "Rhofade (oxymetazoline hydrochloride) cream, For topical use only"
Controlled drug substance symbol (if applicable)	NA	NA
Dosage Forms and Strengths (201.57(a)(8))	Cream, (b) (4) Each gram of cream contains 10 mg (1%) oxymetazoline HCl, equivalent to 8.8mg (0.88%) of oxymetazoline free base (3)	Not satisfactory. Dosage form is presented correctly. The strength is expressed according to (b) (4). (b) (4) The strength should be revised to 1% (the strength of oxymetazoline hydrochloride).



QUALITY ASSESSMENT



		Revise to “Cream, 1%. Each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8mg (0.88%) of oxymetazoline free base.”
Whether the drug product is scored	NA	NA

(b) “Full Prescribing Information” Section

#3. Dosage Forms and Strengths

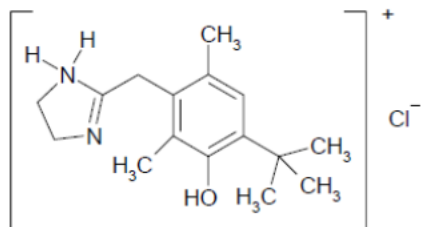
RHOFADE™ (oxymetazoline (b) (4) cream, (b) (4)%, is a white to off-white cream (b) (4) Each gram of topical cream contains 10 mg (1%) oxymetazoline HCl, equivalent to 8.8mg (0.88%) of oxymetazoline free base.

Item	Information Provided in NDA	Reviewer’s Comment and Recommendations
Available dosage forms	RHOFADE™ (b) (4) cream	Not Satisfactory. The Established name is not correct. Remove (b) (4) from the dosage form.
Strengths: in metric system	RHOFADE™ (b) (4) cream, (b) (4), is a white to off-white cream (b) (4) Each gram of topical cream contains 10 mg (1%) oxymetazoline HCl, equivalent to 8.8mg (0.88%) of oxymetazoline free base.	Not satisfactory. The dosage strength is presented in (b) (4) Revise it to be consistent with the hydrochloride salt form. Spell out HCl to hydrochloride. This applies to in the whole document. Revise to RHOFADE™ (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. Each gram of the cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8mg (0.88%) of oxymetazoline free base.
Active moiety expression of strength with equivalence statement (if applicable)	Each gram of topical cream contains 10 mg (1%) oxymetazoline HCl, equivalent to 8.8mg (0.88%) of oxymetazoline free base.	Satisfactory. Equivalence statement included. See comments above.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	RHOFADE™ (b) (4) cream, (b) (4), is a white to off-white cream (b) (4)	Not Satisfactory. Review team decided to remove (b) (4)

#11: Description**11 DESCRIPTION**

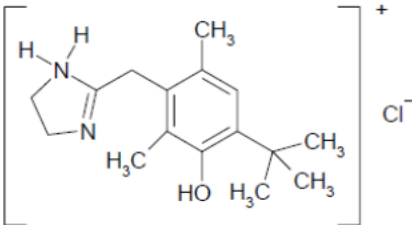
RHOFADE™ (b) (4) cream (b) (4) contains oxymetazoline (b) (4)

(b) (4) **RHOFADE™** (b) (4) is a white to off-white cream. It has a chemical name of 3-[(4,5-Dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethyl-phenol hydrochloride and a molecular weight of 296.8. The molecular formula of oxymetazoline HCl is C₁₆H₂₅(b) (4)N₂O and its structural formula is:



Each gram of **RHOFADE™** (b) (4) cream contains 10 mg (1%) oxymetazoline (b) (4) equivalent to 8.8 mg (0.88%) of oxymetazoline free base. The cream contains the following inactive ingredients: (b) (4), (b) (4), butylated hydroxytoluene, anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol 300, PEG-6 stearate, glycol stearate, PEG-32 stearate, cetostearyl alcohol, cetareth-6, stearyl alcohol, cetareth-25, methylparaben, propylparaben, phenoxyethanol, and purified water.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	RHOFADE™ (b) (4) cream	Not satisfactory. Revise to "RHOFADE™ (oxymetazoline hydrochloride) cream"
Dosage form and route of administration	RHOFADE™ (b) (4) cream (b) (4)	Not Satisfactory. Remove (b) (4) See comments in previous section.
Active moiety expression of strength with equivalence statement (if applicable)	Each gram of RHOFADE™ (b) (4) cream contains 10 mg (1%) oxymetazoline HCl, equivalent to 8.8 mg (0.88%) of oxymetazoline free base.	Not satisfactory. Equivalence statement included but it needs to be revised to use oxymetazoline hydrochloride as the established name and free base form in the equivalence statement. See previous

Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The cream contains the following inactive ingredients: (b) (4), butylated hydroxytoluene, anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol 300, PEG-6 stearate, glycol stearate, PEG-32 stearate, cetostearyl alcohol, cetareth-6, stearyl alcohol, cetareth-25, methylparaben, propylparaben, phenoxyethanol, and purified water.	comments. Not satisfactory. (b) (4) should be sodium citrate dihydrate; (b) (4) should be citric acid anhydrous; (b) (4) should be disodium edetate dihydrate; Revise the following: (b) (4) to "sodium citrate dihydrate"; (b) (4) to "citric acid anhydrous"; (b) (4) to "disodium edetate dihydrate".
Statement of being sterile (if applicable) Pharmacological/ therapeutic class	N/A (b) (4)	NA Not Satisfactory. Revise to an α_{1A} adrenoceptor agonist. This is based on the clinical team recommendation. See package insert document.
Chemical name, structural formula, molecular weight	It has a chemical name of 3-[(4,5-Dihydro-1H-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethyl-phenol hydrochloride and a molecular weight of 296.8. The molecular formula of oxymetazoline HCl is $C_{16}H_{21}N_2O$ and its structural formula is: 	NotSatisfactory. Correct the expression for Cl. (Cl is not (b) (4))
If radioactive, statement of important nuclear characteristics.	N/A	NA
Other important chemical or physical properties (such as pKa or pH)	Not provided	Not satisfactory. Comment: Provide important chemical or physical properties for the drug substance oxymetazoline hydrochloride.

#16: How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

RHOFADE™ (b) (4) cream, (b) (4) is a white to off-white cream, (b) (4)

NDC 0023-5300-30 30 gram (b) (4) tubes

NDC 0023-5300-60 60 gram (b) (4) tubes

NDC 0023-5300-35 30 gram (b) (4) pump (b) (4)

NDC 0023-5300-65 60 gram (b) (4) pump (b) (4)

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

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Irvine, CA 92612

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Patented. See: www.allergan.com/products/patent_notices

Made in the U.S.A.



Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	RHOFADE™ (b) (4) cream, (b) (4)	Not Satisfactory. Established name is not correct. Revise to "RHOFADE™ (oxymetazoline hydrochloride) cream, 1%."
Available units (e.g., bottles of 100 tablets)	RHOFADE™ (b) (4) cream, (b) (4) is a white to off-white cream, (b) (4)	Not Satisfactory. (b) (4)

	(b) (4) 30 gram (b) (4) tubes 60 gram (b) (4) tubes 30 gram (b) (4) pump (b) (4) 60 gram (b) (4) pump (b) (4)	(b) (4) Revise to RHOFADE™ (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. The product is available in tubes and pump bottles and is supplied in the following packaging configurations, each with a child-resistant closure: ...
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	a white to off-white cream NDC 0023-5300-30 30 gram (b) (4) tubes NDC 0023-5300-60 60 gram (b) (4) tubes NDC 0023-5300-35 30 gram (b) (4) pump (b) (4) NDC 0023-5300-65 60 gram (b) (4) pump (b) (4)	Satisfactory. The NDA# is displayed. A description of the dosage form is provided.
Storage conditions	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].	Satisfactory.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	(b) (4)	Satisfactory.



QUALITY ASSESSMENT



Reviewer's Assessment:

To maintain consistency with other dosage forms of the same active ingredient oxymetazoline hydrochloride, ONDP recommends retaining the salt in the drug product established name as “(oxymetazoline hydrochloride) cream”. This is in accordance with the exception rules (C) in CDER salt policy, “Naming of Drug Products Containing Salt Drug Substances” (June 2015).

1. Oxymetazoline has a long history as the active moiety in the marketed human drug (e.g. OTC drugs OCUCLEAR, Vision L.R. and Rx drug KOVANAZE (tetracaine HCl and oxymetazoline HCl) Nasal Spray).
2. The established names for the existing USP monographs are using oxymetazoline hydrochloride, e.g. Oxymetazoline Hydrochloride, Oxymetazoline Hydrochloride Nasal Solution, and Oxymetazoline Hydrochloride Ophthalmic Solution.

Recommendation:

Regarding PI, the following deficiencies should be resolved before approval of this application.

A. Highlight Section

1. The established name is not presented correctly. Per Product Title Guidance, the correct presentation should be “Rhofade (oxymetazoline hydrochloride) cream. **For topical use** (b) (4).” Please revise throughout the prescribing information (PI).
HCl should be spelled out throughout the PI document. Please revise throughout the prescribing information.
2. Dosage Form and Strengths:
Revise to “Cream, 1%.
Each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8mg (0.88%) of oxymetazoline free base”
Remove (b) (4) from the dosage form throughout the PI document.

B. Full Prescribing Information

#3 Dosage Form and Strengths:

1. Revise to “RHOFADE™ (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. Each gram of topical cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8mg (0.88%) of oxymetazoline free base.”
2. Revise the dosage form statement from (b) (4) to read “cream”.

#11 Description

1. The established name is not presented correctly. Revise to “Rhofade™ (oxymetazoline hydrochloride) cream”
2. Inactive ingredient: Revise the following: (b) (4) to “sodium citrate dihydrate”; (b) (4) to “citric acid anhydrous”; (b) (4) to “disodium edetate dihydrate”.
3. Provide important chemical or physical properties for the drug substance oxymetaxoline HCl.
4. Oxymetazoline hydrochloride pharmacological class needs to be revised according to the clinical recommendation. Revise to “RHOFADE (oxymetazoline hydrochloride) cream, 1% contains oxymetazoline hydrochloride, an α_{1A} adrenoceptor agonist.”
5. Correct the expression for Cl. (Cl is not (b) (4))

#16 How Supplied/Storage and Handling

1. The established name is not correct. **Revise to**
RHOFADE™ (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. (b) (4)
...
...

2. Immediate Container Label

8 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 Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Rhofade™ (b) (4) cream, (b) (4)	Not Satisfactory. The established name is not correct. Revise to "Rhofade™ (oxymetazoline hydrochloride) cream"
Dosage strength	Rhofade™ (b) (4) (b) (4) cream (b) (4)	Not Satisfactory. It did not express per the active ingredient as salt form. (b) (4) " needs to be removed. Revise to "Rhofade™ (oxymetazoline hydrochloride) cream, 1% "
Net contents	30 g 60 g	Satisfactory. The net content amounts are expressed in accordance with their respective targeted amount of 30g or 60g.
"Rx only" displayed prominently on the main panel	Rx Only	Satisfactory.
NDC number (21 CFR 207.35(b)(3)(i))	NDC 0023-5300-35	Satisfactory. Each configuration provided a unique NDC number. NDC number for 30 g pump manufactured at DPT lab is shown as an example.
Lot number and expiration date (21 CFR 201.17)	Lot: Exp:	Satisfactory. There is a space holder
Storage conditions	Storage: Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].	Satisfactory.
Bar code (21CFR 201.25)	Not specified.	Satisfactory. Bar code is not provided in the immediate container label. It is provided in the carton, therefore it is acceptable.
Name of manufacturer/distributor	Manufactured for Allergan, Irvine, CA 92612, U.S.A. By DPT Laboratories, Ltd, San Antonio, TX 78215 © 2016 Allergan. All rights reserved. All trademarks are the property of their respective	Satisfactory.

	owners. Patented. See: www.allergan.com/products/patent_notices Made in U.S.A. Or © 2016 Allergan. All rights reserved. Irvine, CA 92612, U.S.A. All trademarks are the property of their respective owners. Patented. See: www.allergan.com/products/patent_notices Made in U.S.A.	
And others, if space is available		

Reviewer's Assessment:

The followings related to the container labels need to be resolved:

1. Revise the drug product title and its strength as follows:
Rhofade (oxymetazoline hydrochloride) cream, 1%.
In addition, the strength equivalency statement based on the active moiety, oxymetazoline, should also be included in the label.
2. Revise the dosage form statement from (b) (4) to read "cream".
3. Ensure the presentation of the established name on all panels is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). (This comment has been coordinated with DMEPA).
4. The following inactive ingredients should be revised to include the solid forms: (b) (4) should be revised to "sodium citrate dihydrate"; (b) (4) to "citric acid anhydrous"; (b) (4) to "disodium edetate dihydrate".

3. Carton Labeling

8 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 Comment and Recommendations
Proprietary name, established name (font size, prominence)	Rhofade™ (b) (4) cream	Not Satisfactory. The established name is not correct. Remove (b) (4) Revise to “Rhofade™ (oxymetazoline hydrochloride) cream”
Dosage strength	(b) (4)	Not Satisfactory. The dose strength needs to be revised to 1%. This is to be consistent with the established name “oxymetazoline hydrochloride”.
Net quantity of dosage form	30 g	Satisfactory. Only one example of 30 g is listed in the review column.
“Rx only” displayed prominently on the main panel	Rx Only	Satisfactory.
Lot number and expiration date	LOT: EXP.:	Satisfactory.
Storage conditions	Storage: Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].	Satisfactory.
Bar code (21CFR 201.25)	A placeholder is provided.	Satisfactory. Provided a place holder.
NDC number (21 CFR 207.35(b)(3)(i))	NDC 0023-5300-35 (30 g pump manufactured by (b) (4))	Satisfactory. Unique NDA# is provided for each configuration according to the

		container and content (pump, tube, 30g or 60g.)
Manufacturer/distributor's name	© 2016 Allergan. All rights reserved. Irvine, CA 92612, U.S.A. Made in U.S.A. or Manufactured for Allergan, Irvine, CA 92612, U.S.A. By DPT Laboratories, Ltd, San Antonio, TX 78215	Satisfactory.
Quantitative ingredient information (injectables)	Each gram of RHOFADE™ (b) (4) cream contains 10 mg (1%) oxymetazoline (b) (4) equivalent to 8.8 mg (0.88%) of oxymetazoline free base, with the inactive ingredients (b) (4) (b) (4) butylated hydroxytoluene, anhydrous lanolin, medium chain triglycerides, diisopropyl adipate, oleyl alcohol, polyethylene glycol 300, PEG-6 stearate, glycol stearate, PEG-32 stearate, cetostearyl alcohol, cetareth-6, stearyl alcohol, cetareth-25, methylparaben, propylparaben, phenoxyethanol, and purified water.	Not Satisfactory. (b) (4) should be revised to “sodium citrate dihydrate”; (b) (4) to “citric acid anhydrous”; (b) (4) to “disodium edetate dihydrate”.
Statement of being sterile (if applicable)	NA	NA
“See package insert for dosage information”	Dosage: Apply a pea-sized amount once daily in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin, avoiding the eyes and lips.	Satisfactory. There is a dose instruction included. The following information should be included for pump

		configuration: “Important: Prime pump before initial use and discard the product from the first three pumps.” (Also see the comments from DMEPA)
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	(b) (4)	Satisfactory.

Reviewer’s Assessment:

The following comments should be resolved:

1. The established name is not correct. Revise to “Rhofade™ (oxymetazoline hydrochloride) cream”
2. The dosage strength needs to be revised and correlated to the established name (HCl salt form). Revise (b) (4) to “1%”. The salt equivalency statement needs to be included: equivalent to 0.88% of oxymetazoline.
3. Ensure the presentation of the established name on all panels is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). (This comment has been coordinated with DMEPA).
4. The following inactive ingredients should be revised to include the solid forms: (b) (4), should be revised to “sodium citrate dihydrate”; (b) (4) to “citric acid anhydrous”; (b) (4) to “disodium edetate dihydrate”.
5. For pump configuration, the following information should be included: “Important: Prime pump before initial use and discard the product from the first three pumps.” (This comment has been coordinated with DMEPA).

Overall Assessment and Recommendation:

Allergen submitted a NDA 208552 with drug product Rhofade™ (b) (4) cream 1%, for treatment of persistent facial erythema associated with rosacea, in adults (b) (4). The proposed proprietary (trade) name is Rhofade™. It is administered by the topical route only with a pea-sized amount daily.

The following materials related to labeling/label have been reviewed from CMC perspective:

1. Names and Dosage Forms and Strengths in the Highlights of Prescribing Information
2. #3 (Dosage Forms and Strengths), #11 Description and #16 (How Supplied/Storage and Handling) in the Full Prescribing Information
3. Container label and Carton Label for both strengths of the drug product.
4. Only the labels (container and carton) of 30g and 60g tube and pump container configurations manufactured at both DPT and (b) (4) are reviewed. The labels of 3g physician samples are not reviewed.

The applicant proposed oxymetazoline as the established name for drug product Rhofade (b) (4) is not acceptable. After carefully examination of the relevant USP, FDA policies and the market history of desmopressin acetate as a human drug, the recommended established name of the drug product for Rhofade (b) (4) cream is “(oxymetazoline HCl) cream”. Retaining the salt (hydrochloride) in the established name is based on the exception rules according to FDA Guidance for Industry “Naming of Drug Products Containing Salt Drug Substances” (June 2015). Oxymetazoline hydrochloride as the active ingredient is available as the marketed drug with dosages forms of ophthalmic drop and nasal spray. Other detailed deficiencies are listed below. Based on the above assessments, this NDA is not recommended for approvals from the ONDP perspective due to unresolved CMC label/labeling issues as delineated below.

Note: Due to the voluntarily withdrawal of (b) (4) manufacture site by the applicant, the labeling information provided to the (b) (4) site products do not apply to NDA208552 approval at this time. Details see the facility reviewer comment.

List of Deficiencies:

The following deficiencies should be resolved before approval of this application.

I. Regarding PI**A. Highlight Section**

1. The established name should be revised to “Rhofade (oxymetazoline hydrochloride) cream. For topical use only.” Please revise throughout the prescribing information (PI).
HCl should be spelled out throughout the PI document.
2. Dosage Form and Strengths:
Revise to “Cream. (b) (4)”. Revise the dosage form to “Cream” throughout the PI document.
Revise to each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8mg (0.88%) of oxymetazoline free base”

B. Full Prescribing Information**#3 Dosage Form and Strengths:**

1. Revise to “**RHOFADE™** (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. Each gram of cream contains 10 mg (1%) oxymetazoline hydrochloride, equivalent to 8.8mg (0.88%) of oxymetazoline free base.”
2. Revise the dosage form statement from (b) (4) to read “cream”.
3. Remove (b) (4)

#11 Description

1. The established name should be revised to “Rhofade™ (oxymetazoline hydrochloride) cream”
2. The following inactive ingredients should be revised to include the solid forms: (b) (4), to “sodium citrate dihydrate”; (b) (4) to “citric acid anhydrous”; (b) (4) to “disodium edetate dihydrate”.
3. Provide important chemical or physical properties for the drug substance oxymetaxoline HCl.

4. Pharmacological class needs to be revised to “RHOFADÉ (oxymetazoline hydrochloride) cream, 1% contains oxymetazoline hydrochloride, an α_{1A} adrenoceptor agonist.”
5. Correct the expression for Cl (Cl is not (b) (4)).

#16 How Supplied/Storage and Handling

1. The established name is not correct. **Revise to**
 RHOFADÉ™ (oxymetazoline hydrochloride) cream, 1%, is a white to off-white cream. (b) (4)
 ...

II. Regarding Container/Carton Label

1. Revise the drug product title and its strength to the following:
 Rhofade (oxymetazoline hydrochloride) cream, 1%
 In addition, the strength equivalency statement based on the active moiety, oxymetazoline , should also be included in the label.
2. The name of following inactive ingredients should be revised to reflect the excipients actually used:
 (b) (4) should be revised to “sodium citrate dihydrate”; (b) (4) should be revised to “citric acid anhydrous”; (b) (4) should be revised to “disodium edetate dihydrate”.
3. Ensure the presentation of the established name on all panels is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
4. Revise the dosage form statement from (b) (4) to read “cream”.
5. For pump configuration, the following information should be included: “Important: Prime pump before initial use and discard the product from the first three pumps.”

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

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

I agree with Dr. Cai's assessment on the labeling and labels with the statement that this application is not ready for approval until the deficiencies are resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP



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QUALITY ASSESSMENT



BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of Rhofade (oxymetazoline HCl) Cream, (b) (4), under the 505(b)(1) path. Rhofade Cream is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

NDA: 208552

Drug Product Name / Strength: Oxymetazoline HCl Cream, (b) (4) %

Route of Administration: Topical

Applicant Name: Allergan, Inc.

Review Summary: The pilot scale (b) (4) of the drug product was used in Phase 3 clinical trials and registration stability studies. The batch size of the commercial production will be (b) (4). The Applicant plans to add (b) (4)

(San Antonio, TX). The following assessments were evaluated to support (b) (4) DPT Laboratories as an alternate manufacturing site:

(b) (4)

(
b
)

(b) (4)

The primary site, DPT Laboratories (San Antonio, TX) will be used to manufacture the commercial drug product.

(b) (4)

(b) (4)

From the Biopharmaceutics perspective, NDA 208552 for Rhofade (oxymetazoline HCl) Cream, (b) (4) % is **acceptable**.

List Submissions being reviewed:

March 23, 2016 (Original)

June 28, 2016 (Response to Information Request)

July 22, 2016 (Response to Information Request)

August 18, 2016 (Response to Information Request)

November 30, 2016 (Amendment to a Pending Application: Withdrawal of (b) (4) alternate drug product manufacturing site)

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: (b) (4)

BCS Designation

Reviewer's Assessment: The drug product is a topical cream; therefore, BCS designation is not pertinent to this application.

Solubility:

Permeability:

Dissolution: N/A

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: N/A

Clinical relevance of drug release method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: N/A

Application of drug release/IVIVC in QbD

Reviewer's Assessment: N/A



QUALITY ASSESSMENT



Modified Release Oral Drug Products –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: N/A

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: N/A

(b) (4)

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Extended Release Dosage Forms –Extended Release Claim

Reviewer's Assessment: N/A

Bridging of Formulations

Reviewer's Assessment: The composition of the drug product used in pivotal Phase 3 clinical studies is same as the commercial formulation. Therefore, bridging studies are not required.

Biowaiver Request

Reviewer's Assessment: N/A

Regional Information

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

List of Deficiencies:

There are no deficiencies.

(b) (4)

(b) (4)

(b) (4)

Primary Biopharmaceutics Reviewer Name and Date:

Kelly M. Kitchens, Ph.D., October 18, 2016 (original review)

Kelly M. Kitchens, Ph.D., December 9, 2016 (November 30, 2016 amendment)

Secondary Reviewer Name and Date:

Vidula Kolhatkar, Ph.D., October 19, 2016 (original review)

Vidula Kolhatkar, Ph.D., December 9, 2016 (November 30, 2016 amendment)



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Kolhatkar

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CHAPTER VI: Review of Quality Microbiology

MICROBIOLOGY**Product Background: -****NDA:** 208552**Drug Product Name / Strength:** RHOFADÉ, Oxymetazoline HCl, 1%**Route of Administration:** Topical cream**Applicant Name:** Allergan, Inc.**Manufacturing Site:** DPT Laboratories, San Antonio, TX; Allergan, Inc., Waco, TX**Method of Sterilization:** Not applicable, this is a non-sterile drug product.**Review Summary:** Recommended for Approval.**List Submissions being reviewed:** 3/23/2016, 6/28/2016**Highlight Key Outstanding Issues from Last Cycle:** N/A**Concise Description Outstanding Issues Remaining:** N/A**Supporting/Related Documents:** N/A**Remarks Section:** N/A**S Drug Substance**

Not applicable.

P.1 Description of the Composition of the Drug Product

- Description of drug product – White to off-white cream.
- Drug product composition –

Component	Concentration (% w/w)
Oxymetazoline HCl	1.0
Methylparaben	(b) (4)
Propylparaben	
Phenoxyethanol	
Sodium citrate dehydrate	
Citric acid anhydrous	
Disodium edetate dehydrate	
Butylated hydroxytoluene	

Anhydrous lanolin	(b) (4)	
Medium chain triglycerides		
Diisopropyl adipate		
Oleyl alcohol		
Polyethylene glycol 300		
(b) (4)		
Cetostearyl alcohol		
(b) (4)		
Purified water		

- Description of container closure system –

Container Type	Manufacturer
30 mL aluminum foil laminate tube with child-resistant closure	(b) (4)
60 mL aluminum foil laminate tube with child-resistant closure	
3 mL aluminum foil laminate tube	
30 mL airless pump with child-resistant closure	
60 mL airless pump with child-resistant closure	

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Not applicable, container closure integrity is not required for a non-sterile product.

Antimicrobial Effectiveness Testing

(Microbiological Attributes.pdf)

(b) (4)
AET was performed per USP <51> with samples at 50%, 80%, and 100% of the target concentrations (b) (4)
The microbial enumeration results were not provided but the applicant states that all samples met the acceptance criteria per USP <51> (Microbiological Attributes.pdf, page 2 of 2).

Reviewer's Assessment:

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

DPT Laboratories, Ltd.
307 E. Josephine Street
San Antonio, TX 78215

(b) (4)

**Microbiological release/stability testing**

(b) (4)



Allergan Pharmaceuticals
Castlebar Road, Westport
Co. Mayo, Ireland

P. 3.3 Description of the Manufacturing Process and Process Controls**Overall Manufacturing Operation**

(Description of Manufacturing Process and Process Controls.pdf; Manufacturing Process Development.pdf; Draft Master Validation Plan - (b) (4).pdf)

The pilot batches were produced in the DPT facility and commercial production will take place in the (b) (4) facility. Executed batches are provided from both facilities.

Commercial batch size: (b) (4) kg

The maximum holding periods during manufacturing are not specified.

Reviewer's Assessment: The applicant doesn't provide maximum holding periods but the provided executed batches meet the stated microbial limits. Additionally, the drug product contains (b) (4). The applicant's manufacturing process is consistent with regulatory expectations for a non-sterile aqueous oral product.

P. 3.5 Process Validation and/or Evaluation

P.5 Control of Drug Product

P. 5.1 Specifications

(Specifications.pdf)

Microbial Limits

Total yeast and molds count:	NMT (b) (4) CFU/g
Total aerobic microbial count:	NMT (b) (4) CFU/g
Absence of Specified Organisms:	<i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>B. cepacia</i>

Testing is performed per USP <61> and <62>.

Reviewer's Assessment: The specifications for microbial enumeration and the absence of *E. coli* and *P. aeruginosa* are consistent with those suggested in USP <1111> for a topical product. The applicant describes adequate controls to detect potential contamination with *B. cepacia*.

P.5.2 Analytical Procedures: See Section 5.1

P.5.3 Validation of Analytical Procedures: N/A

P.7 Container Closure: See Section P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(Stability Summary and Conclusions.pdf)

Expiry: (b) (4) months in the airless pumps and 30 mL and 60 mL laminate tubes.
(b) (4) months in the 3 mL laminate tube.

Testing was performed per USP <61> and <62>.

Microbial Limits

Total yeast and molds count:	NMT (b) (4) CFU/g
Total aerobic microbial count:	NMT (b) (4) CFU/g
Absence of Specified Organisms:	<i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>B. cepacia</i>

Samples for long-term stability (25 °C/60% RH) for microbiological testing are taken at 0 and 0, 12, and 24 months. Acceptable results were provided for multiple lots of the drug product in each of the proposed container-closures (3.2.P.8.3).

Reviewer's Assessment: The applicant has met the regulatory expectations regarding microbiological tests and sampling frequencies for the stability program associated with the subject drug product.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(Post-approval Stability Protocol and Stability Commitment.pdf)

The applicant commits to add one batch of three product strengths annually to the long term stability program.

Reviewer's Assessment: The applicant has met the regulatory expectations regarding the post-approval stability protocol.

P.8.3 Stability Data: See Section P.8.1.

A Appendices

A.2 Adventitious Agents Safety Evaluation

The drug product contains lanolin

(b) (4)

The applicant has provided a statement in the Adventitious Agent Safety Evaluation Report in Module 3.2.A.2 indicating that the product does not contain any bovine or caprine material and states that the product complies with guidance Section 6.7 Wool Derivatives.

Reviewer's Assessment: The applicant has met the regulatory expectations regarding adventitious agents.

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable.

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable.

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable.

R Regional Information

Executed Batch Records

Executed batch records were provided for multiple lots produced in both facilities and in all proposed container-closures.

Reviewer's Assessment: The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols: No CP was included in the application.

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

2.A. Package Insert

- Store at 20-25 °C. Excursions permitted to 15-30 °C.

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: Julie Nemecek, 7/5/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
"I concur" should be sufficient



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CHAPTER VIII: CDRH Consult Review on the Non-metered Dose Pump

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 3, 2016
From: Keith Marin, Senior Regulatory Research Reviewer, WO66, RM 2604,
ODE/DAGRID/GDHB
To: Grafton Adams, Senior Regulatory Health Program Manager,
CDER/OPQ/OPRO/DRBPMI/RBPMBI
Subject: CDRH Consult, NDA 208552, ICC (b) (4) DMF (b) (4) Final Review, Rhofade
Cream non-meter dose pump

1. Summary and Recommendation

Based on information reviewed NDA 208552, the sponsor has provided sufficient information related to the bench performance testing, biocompatibility, sterility, shelf life, and shipping studies to support safety of the device. As a result, CDRH/ODE recommends approval for the NDA for this combination product.

The sponsor has identified the following design and release specifications:

Design Specification:

Component	Material Type	Material Details
(b) (4)		

Release Specification:

Test (unit)	Method	Acceptance Criteria at Release	Acceptance Criteria during Shelf Life
Minimum Fill	USP <755>	Meets current compendial acceptance criteria	Not performed
Pump Functionality ^a	Actuating and Weighing		
Number of actuations to prime		Average NMT (b) (4) No individual value greater than (b) (4)	Average NMT (b) (4) No individual value greater than (b) (4)
Amount dispensed per actuation (g)		NLT (b) (4)	NLT (b) (4)
Total amount of drug product dispensed (g)		Average net content NLT labeled amount Net content of any single container NLT (b) (4) labeled amount	Average net content NLT labeled amount Net content of any single container NLT (b) (4) labeled amount

^a Applicable to only pumps

We recommend that the CDER review division confirm that the performance specifications are adequately valid for the patients and medication being delivered.

2. Purpose of Memo

The Center for Drug Evaluation and Research (CDER) has requested a review from the Center for Devices and Radiological Health (CDRH), regarding NDA 208552. The device constituent of this combination product consists of a non-metered pump to deliver Rhofade cream for the treatment of persistent facial erythema associated with rosacea.

Reviewer's Note: The sponsor has stated that they intend to package the drug into two pump containers, a 30g/30 mL dosage and a 60g/60mL dosage (which will be the focus of this review). They also intend to provide the drug in 30mL and 60mL laminate tubes and a 3g/3mL professional sample laminate tube that will be deferred to CDER.

3. Introduction

Allergan is submitting this application for a topical cream formulation of oxymetazoline hydrochloride (HCl) 1.0%, for treatment of persistent facial erythema associated with rosacea, in adults aged 18 years or older. Oxymetazoline is a synthetic, direct-acting, imidazoline-type sympathomimetic agonist that is highly selective for the α 1A adrenoceptor over other α 1 adrenoceptors and non-selective for the α 2 adrenoceptors. As such, oxymetazoline is a potent vasoconstrictor of the cutaneous microvasculature. While the pathophysiology of rosacea remains largely unknown, abnormal flushing and persistent erythema have been theorized to arise from a dysregulation in the cutaneous vasomotor response which, when triggered by environmental stimuli, results in an abnormal and persistent dilation of facial blood vessels.

Allergan has completed the clinical development program for oxymetazoline HCl cream 1.0% in patients with moderate to severe persistent erythema associated with rosacea. The development program comprised 14 studies: 2 pivotal phase 3 studies (199201-004 and -005), a phase 2 dose ranging study (199201-002), a long-term (1-year) safety study (199201-006), a nondrug study to validate the CEA scale used in the pivotal studies (199201-003), and 9 phase 1 and phase 2 studies to assess phototoxicity, bioavailability, pharmacokinetics, pharmacodynamics, and dermal safety.

The recommended dosage and administration of oxymetazoline HCl cream 1.0% is the same as used in the pivotal phase 3 studies and the long-term phase 3 safety study. The sponsor is proposing the administration of approximately a pea-sized amount of medication is applied via a non-metered dose pump once daily in a thin layer to cover the entire face, including forehead, nose, each cheek, and chin.

Product	Indication for Use
Rhofade™ (oxymetazoline) topical cream	RHOFADE™ (oxymetazoline) topical cream, 0.88% is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults

Reviewer's Note: The sponsor has included drug preparation or patient instructions for use.

4. Documents

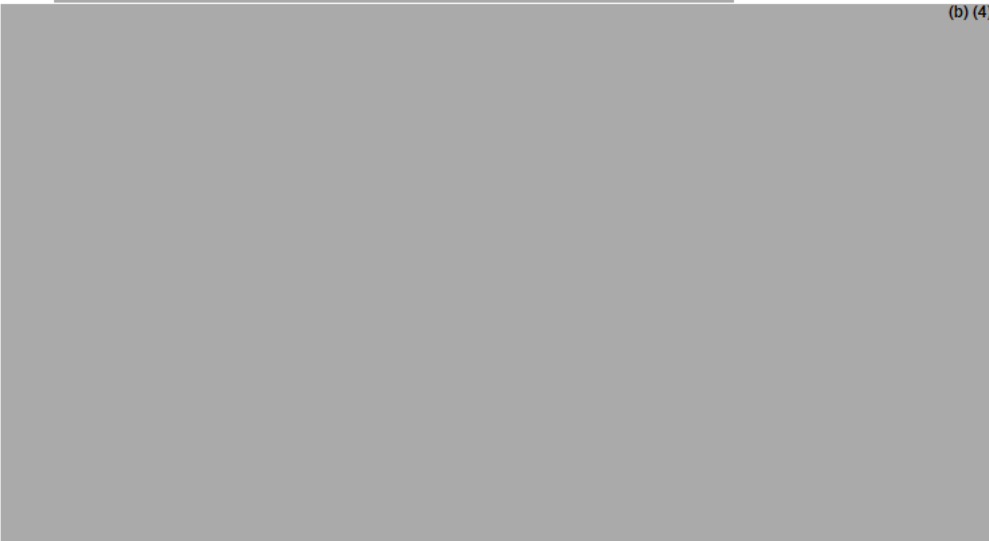
Documentation for the device constituent was obtained from NDA 208552, eCTD location 3.2.P.2, 3.2.P.7, 3.2.R.5 and 3.2.R.6. Also reviewed were the package labeling and medication guide.

5. Device Description

Information on the sarilumab pre-filled syringe was obtained from NDA 208552, eCTD Section 3.2.P.7.

The container closure system selected for the commercial configuration of Oxymetazoline HCl Cream, 1.0% is a 30 mL and 60 mL non-metered airless pump container closure system (CCS) with CRC. The airless pump CCS consists of polypropylene bottles with high density polyethylene

(b) (4) a pump actuator assembly (consisting of (b) (4) and (b) (4) CRC. The bottles contain a (b) (4) All bottle sizes use the same pump actuator assembly (consisting of (b) (4) and (b) (4) cap. This container closure system is manufactured by (b) (4)



Component Number (1-8)	Component Description
(b) (4)	

Reviewer's Note: The sponsor has stated that the details on the airless pump CCS can be found in DMF (b) (4). The sponsor has provided the letter of authorization (LOA) to reference the non-metered airless pump CCS.

Materials

The (b) (4) and product contacting materials of the primary packaging container have been tested to USP <87> and USP <661> requirements and shown to be suitable for dermal pharmaceutical use. All bottle sizes have the same inner and outer diameters, and utilize the same pump. The only difference is in the length of the bottle. A summary description of the container closure component is presented in the table below:

Component Name	Product Contact	Material	Supplier
Airless pump, round	(b) (4)		(b) (4)
30 mL, 60 mL container, round			

Referenced DMF for non-metered airless pump container closure system (CCS)

The primary packaging components in direct contact with the product are subject of Drug Master File (DMF) by the suppliers. Supplier names and DMF references are listed below:

Component	Vendor	Address	DMF
Airless Pump and Bottle system	(b) (4)		

Contact for FDA Correspondence for DMF Holder (b) (4)

Reviewer's Note: The sponsor has referenced DMF (b) (4) for the airless pump CCS and provided the LOA to reference it.

6. Device Functional Testing

The (b) (4) pump design was selected as the commercial configuration for Oxymetazoline HCl Cream, 1.0%. The selection of (b) (4). The commercial packaging configuration for Oxymetazoline HCl Cream, 1.0% will be a 30 mL and 60 mL (b) (4) airless pump system.

(b) (4)



(b) (4)



Materials:

Reviewer's Note: The sponsor has provided a list of materials but no biocompatibility has been provided for the device. As the material inside the device is the same as what is present outside, this will be deferred to the CMC reviewer who will evaluate the extractable & leachables of the drug/device. It is my belief that no additional biocompatibility testing would be needed.

Functional Testing

Review of DMF (b) (4) appears that there is no functional testing for the (b) (4). The only testing present is dosage testing using the (b) (4). However, the sponsor has appeared to validate pump functionality within the NDA through the stability studies at 0, 12, 24, and 36 month time points (with 0 and 12 months

appearing in study) at 25 °C/60% RH and 0, 12, and 34 month time points at 30 °C/65% RH (with 0 and 12 month appearing in study). Pump functionality assessment includes the number of actuations for priming, amount dispensed per actuation, and total amount of drug product delivered. Detailed pump data can be found below:

Table 37 Long Term (25 °C/60% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot-	Orientation	Fill Size (g)		Test Interval	
					0 month	12 month
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Horizontal	30 g	Individual		
				Average		
		Upright	60 g	Individual		
				Average		
		Horizontal	60 g	Individual		
				Average		
Amount Dispensed per actuation (g)	(b) (4)	Upright	30 g	Actuation 11-20 (after priming)	(b) (4)	
		Horizontal	30 g	Actuation 11-20 (after priming)		
		Upright	60 g	Actuation 11-20 (after priming)		
		Horizontal	60 g	Actuation 11-20 (after priming)		
Total Amount Drug Product Dispensed (g)	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Horizontal	30 g	Individual		
				Average		
		Upright	60 g	Individual		
				Average		
		Horizontal	60 g	Individual		
				Average		

Table 38 Long Term (25 °C/60% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval	
					0 months	12 months
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Upright	60 g	Individual		
				Average		
Amount Dispensed per actuation (g)	(b) (4)	Upright	30 g	Actuation 11-20 (after priming)	(b) (4)	
		Upright	60 g	Actuation 11-20 (after priming)		
Total Amount Drug Product Dispensed (g)	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Upright	60 g	Individual		
				Average		

Table 39 Long Term (25 °C/60% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval	
					0 months	12 months
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Upright	60 g	Individual		
				Average		
Amount Dispensed per actuation (g)		Upright	30 g	Actuation 11-20 (after priming)		
		Upright	60 g	Actuation 11-20 (after priming)		
Total Amount Drug Product Dispensed (g)		Upright	30 g	Individual		
				Average		
		Upright	60 g	Individual		
				Average		

Table 40 Long Term (25 °C/60% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval		
					0 months	12 months	
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)		
				Average			
		Upright	60 g	Individual			
				Average			
Amount Dispensed per actuation (g)		Upright	30 g	Actuation 11-20 (after priming)			
		Upright	60 g	Actuation 11-20 (after priming)			
Total Amount Drug Product Dispensed (g)		Upright	30 g	Individual			
				Average			
		Upright	60 g	Individual			
				Average			
(b) (4)							

Table 41 Long Term (25 °C/60% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval	
					0 months	12 months
Number of pumps required to prime pump	(b) (4)	Upnight	30 g	Individual	(b) (4)	
				Average		
		Upnight	60 g	Individual		
				Average		
Amount Dispensed per actuation (g)		Upnight	30 g	Actuation 11-20 (after priming)		
		Upnight	60 g	Actuation 11-20 (after priming)		
Total Amount Drug Product Dispensed (g)		Upnight	30 g	Individual		
				Average		
	Upnight	60 g	Individual			
			Average			
(b) (4)						

Table 42 Intermediate (30 °C/65% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval	
					0 months	12 months
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Horizontal	30 g	Individual		
				Average		
		Upright	60 g	Individual		
				Average		
		Horizontal	60 g	Individual		
				Average		
Amount Dispensed per actuation (g)	(b) (4)	Upright	30 g	Actuation 11-20 (after priming)		
		Horizontal	30 g	Actuation 11-20 (after priming)		
		Upright	60 g	Actuation 11-20 (after priming)		
		Horizontal	60 g	Actuation 11-20 (after priming)		
Total Amount Drug Product Dispensed (g)	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Horizontal	30 g	Individual		
				Average		
		Upright	60 g	Individual		
				Average		
		Horizontal	60 g	Individual		
				Average		

Table 43 Intermediate (30 °C/65% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval	
					0 months	12 months
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Upright	60 g	Individual		
				Average		
Amount Dispensed per actuation (g)		Upright	30 g	Actuation 11-20 (after priming)		
		Upright	60 g	Actuation 11-20 (after priming)		
Total Amount Drug Product Dispensed (g)		Upright	30 g	Individual		
				Average		
	Upright	60 g	Individual			
			Average			
(b) (4)						

Table 44 Intermediate (30 °C/65% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval	
					0 months	12 months
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Upright	60 g	Individual		
				Average		
Amount Dispensed per actuation (g)		Upright	30 g	Actuation 11-20 (after priming)		
				Upright		60 g
Total Amount Drug Product Dispensed (g)		Upright	30 g			
				Average		
	Upright	60 g	Individual			
			Average			
(b) (4)						

Table 45 Intermediate (30 °C/65% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval	
					0 months	12 months
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)	
				Average		
		Upright	60 g	Individual		
				Average		
Amount Dispensed per actuation (g)		Upright	30 g	Actuation 11-20 (after priming)		
		Upright	60 g	Actuation 11-20 (after priming)		
Total Amount Drug Product Dispensed (g)		Upright	30 g	Individual		
				Average		
		Upright	60 g	Individual		
				Average		
(b) (4)						

Table 46 Intermediate (30 °C/65% RH) Pump Performance Stability Data: Lot (b) (4)

Pump Functionality	Lot	Orientation	Fill Size (g)		Test Interval		
					0 months	12 months	
Number of pumps required to prime pump	(b) (4)	Upright	30 g	Individual	(b) (4)		
				Average			
		Upright	60 g	Individual			
				Average			
Amount Dispensed per actuation (g)		Upright	30 g	Actuation 11-20 (after priming)			
				Upright		60 g	Actuation 11-20 (after priming)
Total Amount Drug Product Dispensed (g)		Upright	30 g				Individual
				Average			
		Upright	60 g	Individual			
				Average			
(b) (4)							

Reviewer's Note: The sponsor has provided functional testing assessing the number of pumps necessary to prime pump, amount dispensed per actuation, and total amount of drug dispensed at 0 and 12 month test intervals. Based on review of the testing, the pump functionality has not changed over the 12 months observed. The testing supports that the pump can be adequately primed, the amount dispensed is appropriate for the dosage to allow for full administration of the medication.

Biocompatibility

The sponsor has provided a listing of materials for the non-metered pump. No biocompatibility testing based on ISO 10993 was located within the DMF or NDA.

Reviewer's note: Discussion with the CMC reviewer, Dr. Hong Cai will also review the extractable and leachable requirements of the pump when filled with the formulation. As the materials on the outside of the pump will not differ from the inside of the pump, I will defer to Dr. Cai's review. The pump is intended to be handled by the user and the cream applied topically; it is my belief that any compatibility issues will be addressed in the review of the extractable and leachable by Dr. Cai.

Shipping Studies

No formal shipping studies have been provided. Allergan has stated that they have not conducted a formal shipping study at this time (b) (4)

(b) (4) as part of process validation. During development, registration stability lots were shipped via a combination of ground and air transportation in intermediate secondary packaging from DPT Labs in San Antonio to (b) (4) and the impact of real-time transportation on the container closure system was assessed. The units received at (b) (4) were assessed visually for container closure

integrity. The sponsor believes that the real-time shipping study provided adequate assurance that the container closure system will withstand the proposed commercial transportation environment

Reviewer's note: CDER was asked whether the formal shipping study would need to be completed before approval. Based on the response by Dr. Cai, their division does not usually need a formal shipping study as long as the proposed storage condition and the permitted reasonable excursion is covered in the stability studies with a favorable outcome. As this device is a low risk device where a device failure would not cause injury to the patient, I do not see any issue with the shipping studies being provided with the final commercial packaging.

Shelf Life

The sponsor has provided a summary of results from stability studies assessing the number of pumps necessary to prime pump, amount dispensed per actuation, and total amount of drug dispensed at 0 and 12 month test intervals.

7. CDRH Comments for Review Team

- Please ensure that a separate consult has been sent to CDRH Office of Compliance to assist with any necessary device facilities inspections required for approval of this NDA.

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- Sterility and extractable/leachables of the drug device will be deferred to CDER.

If you have any questions, please contact LCDR Keith Marin at 301-796-2462.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Keith G. Marin -S Digitally signed by Keith G. Marin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -S, 0.9.2342.19200300.100.1.1=0011250397 Date: 2016.08.03 11:01:18 -04'00'
Branch Chief Sign-Off	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.08.10 14:44:38 -04'00'



Yichun
Sun

Digitally signed by Yichun Sun
Date: 12/13/2016 02:29 52PM
GUID: 507c72be00005c4494de145d79515e1f

