CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205894 Orig1sS000

Trade Name: Cyclosporine Ophthalmic Emulsion, 0.05%.

Sponsor: Mylan Pharmaceuticals Inc.

Approval Date: February 2, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

205894 Orig1sS000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205894 Orig1sS000

APPROVAL LETTER

ANDA 205894

ANDA APPROVAL

Mylan Pharmaceuticals Inc.
3711 Collins Ferry Road
Morgantown, WV 26505
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Wayne Talton:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on November 1, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Cyclosporine Ophthalmic Emulsion, 0.05%.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts.

Reference is also made to the complete response letter issued by this office on September 30, 2020, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug product meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Cyclosporine Ophthalmic Emulsion, 0.05%, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Restasis Ophthalmic Emulsion, 0.05%, of Allergan, Inc. (Allergan).

The RLD upon which you have based your ANDA, Allergan's Restasis Ophthalmic Emulsion, 0.05%, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
8,629,111 (the '111 patent)	August 27, 2024
8,633,162 (the '162 patent)	August 27, 2024
8,642,556 (the '556 patent)	August 27, 2024
8,648,048 (the '048 patent)	August 27, 2024

8,685,930 (the '930 patent)	August 27, 2024
9,248,191 (the '191 patent)	August 27, 2024

Your ANDA contains paragraph IV certifications to each of the patents[1], under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Cyclosporine Ophthalmic Emulsion, 0.05%, under this ANDA. You have notified the Agency that Mylan Pharmaceuticals Inc. (Mylan) complied with the requirements of section 505(j)(2)(B) of the FD&C Act.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts; therefore, we remind you that you must comply with the postmarketing safety reporting requirements for an approved combination product (21 CFR Part 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at: https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with

annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: https://www.fda.gov/media/128163/download).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at: https://www.fda.gov/media/73013/download. Information and Instructions for completing the form can be found at: https://www.fda.gov/media/132152/download. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[2] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling

[21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the Guidance for Industry titled "SPL Standard for Content of Labeling Technical Qs and As" at: https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the Guidance for Industry titled "Changes to an Approved NDA or ANDA" at: https://www.fda.gov/media/71846/download.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] The Agency notes that the '111, '162, '556, '048, '930 and '191 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Anh Pham

Digitally signed by Anh Pham
Date: 2/02/2022 11:36:42AM
GUID: 54e4c56f00060bb2c61b878bc7a7bf95

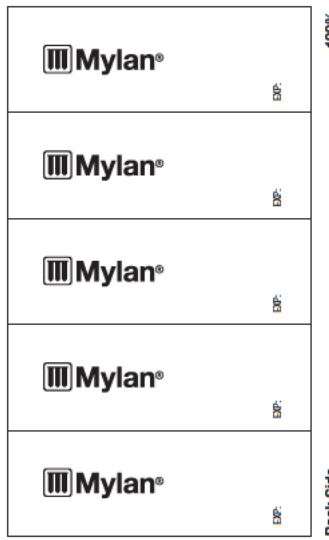
CENTER FOR DRUG EVALUATION AND RESEARCH

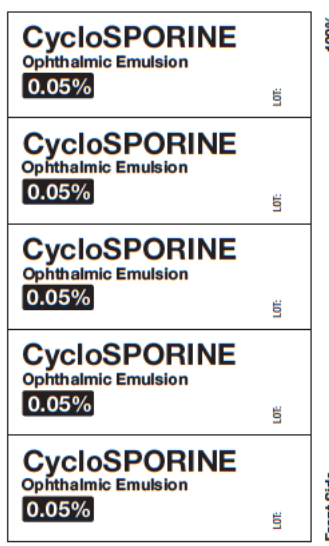
APPLICATION NUMBER:

205894Orig1sS000

LABELING

0.5 mL Single-Use Vials (0.4 mL Fill Volume Each) - Strip of Five Vials





0.75 in
1.5 in
3 in
1.5 in
0.5" Seal Area - No critical art (background only)
0.75" Seal Area - No critical art (background only)
Fold Area - No Critical copy (background only)
CycloSPORINE
Ophthalmic Emulsion
0.05%
FOR USE IN THE EYES
Sterile, Preservative-Free
Rx only
5 Single-Use Vials (0.4 mL Each)
NDC 0378-8760-98
Fold Area - No Critical copy (background only)
Each mL contains:
Active: Cyclosporine, USP 0.05%
Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.
Usual Dosage: Twice daily approximately 12 hours apart. Invert the vial before using. Use immediately after opening and then discard. See accompanying prescribing information.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Store vials in the carton until use.
Code Date
Print Local
0.75" Seal Area - No critical art
(background only, can't interfere with eye contrast)
Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in U.S.A.
Mylan®
Mylan.com
MYL08 01 0001
0.5 in
0.5" Seal Area - No critical art (background only)
0.5 in
5.00" Cut Off
4 in
7.50" Cut Web Width

(b) (4)

(b) (4)

15 3/8
[390.52]

8
[203.2]

MYL1030-442R00

NDC 0378-8760-58

CycloSPORINE
Ophthalmic Emulsion
0.05%

FOR USE IN THE EYES
Sterile, Preservative-Free

Mylan®

Rx only

30 Single-Use Vials (0.4 mL Each)

Each mL contains:
Active: Cyclosporine, USP 0.05%

Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.

Usual Dosage: Twice daily approximately 12 hours apart. Invert the vial before using. Use immediately after opening and then discard. See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Store vials in the carton until use.

The entire contents of the carton (30 vials) must be dispensed intact.

N
3 03788 76058 7

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Made in U.S.A.

Mylan®
Mylan.com

SFRA 00271 E170068

NDC 0378-8760-58

CycloSPORINE
Ophthalmic Emulsion
0.05%

FOR USE IN THE EYES
Sterile, Preservative-Free

Mylan®

Rx only

30 Single-Use Vials (0.4 mL Each)

NDC 0378-8760-58

CycloSPORINE
Ophthalmic Emulsion
0.05%

FOR USE IN THE EYES
Sterile, Preservative-Free

Mylan®

Rx only

30 Single-Use Vials (0.4 mL Each)

NDC 0378-8760-58

CycloSPORINE
Ophthalmic Emulsion
0.05%

FOR USE IN THE EYES
Sterile, Preservative-Free

Mylan®

Rx only

30 Single-Use Vials (0.4 mL Each)

3 3/16
[80.96]

SERIALIZATION
1" x 2 9/16"
BLACK AREA RESERVED FOR ONLINE LASER CODING

WHITE UNCOATED AREA RESERVED FOR INKJET CODING
1" x 2 9/16"

2 1/4
[57.15]

5 1/8
[130.17]

(b) (4)

19⅞
[504.82]

11⅜
[288.92]

3³⁄₁₆
[80.96]

NDC 0378-8760-91

CycloSPORINE
Ophthalmic Emulsion
0.05%
FOR USE IN THE EYES
Sterile, Preservative-Free
Mylan®
Rx only
60 Single-Use Vials (0.4 mL Each)

M Y L 1 060-44 ZR0 0

Each mL contains:
Active: Cyclosporine, USP 0.05%

Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.

Usual Dosage: Twice daily approximately 12 hours apart. Invert the vial before using. Use immediately after opening and then discard. See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Store vials in the carton until use.

The entire contents of the carton (60 vials) must be dispensed intact.

N 3 03788 76091 4

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in U.S.A.

Mylan®
Mylan.com

NDC 0378-8760-91

CycloSPORINE
Ophthalmic Emulsion
0.05%
FOR USE IN THE EYES
Sterile, Preservative-Free
Mylan®
Rx only
60 Single-Use Vials (0.4 mL Each)

NDC 0378-8760-91

CycloSPORINE
Ophthalmic Emulsion
0.05%
FOR USE IN THE EYES
Sterile, Preservative-Free
Mylan®
Rx only
60 Single-Use Vials (0.4 mL Each)

SERIALIZATION
1" x 2⁹⁄₁₆"
BLACK AREA RESERVED FOR ONLINE LASER CODING

WHITE UNCOATED AREA RESERVED FOR INKJET CODING
1" x 2⁹⁄₁₆"

4½
[114.3]

5⅛
[130.17]

0.187" 0.187"

Barcode

Human Readable Text

keep body text out of this area

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CYCLOSPORINE OPHTHALMIC EMULSION 0.05% safely and effectively. See full prescribing information for CYCLOSPORINE OPHTHALMIC EMULSION.

CYCLOSPORINE ophthalmic emulsion 0.05%

For topical ophthalmic use

Initial U.S. Approval: 1983

--------INDICATIONS AND USAGE --------

Cyclosporine ophthalmic emulsion is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs. (1)

----DOSAGE AND ADMINISTRATION----

Instill one drop of cyclosporine ophthalmic emulsion twice a day in each eye approximately 12 hours apart. (2)

---DOSAGE FORMS AND STRENGTHS---

Cyclosporine ophthalmic emulsion 0.5 mg/mL (3)

----------CONTRAINDICATIONS---------

- Hypersensitivity (4)

----WARNINGS AND PRECAUTIONS----

- To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces. (5.1)

---------ADVERSE REACTIONS----------

The most common adverse reaction following the use of cyclosporine ophthalmic emulsion was ocular burning (17%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Cyclosporine ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

2 DOSAGE AND ADMINISTRATION

Invert the unit dose vial a few times to obtain a uniform, white, opaque emulsion before using. Instill one drop of cyclosporine ophthalmic emulsion twice a day in each eye approximately 12 hours apart. Cyclosporine ophthalmic emulsion can be used concomitantly with lubricant eye drops, allowing a 15-minute interval between products. Discard vial immediately after use.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic emulsion containing cyclosporine 0.5 mg/mL

4 CONTRAINDICATIONS

Cyclosporine ophthalmic emulsion is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Eye Injury and Contamination

Be careful not to touch the vial tip to your eye or other surfaces to avoid potential for eye injury and contamination.

5.2 Use with Contact Lenses

Cyclosporine ophthalmic emulsion should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of cyclosporine ophthalmic emulsion.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Potential for Eye Injury and Contamination [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, the most common adverse reaction following the use of cyclosporine opthalmic emulsion was ocular burning (17%).

Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of cyclosporine ophthalmic emulsion. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Clinical administration of cyclosporine ophthalmic emulsion 0.05% is not detected systemically following topical ocular administration [*see Clinical Pharmacology (12.3)*], and maternal use is not expected to result in fetal exposure to the drug. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses [*see Data*].

Data

Animal Data

At maternally toxic doses (30 mg/kg/day in rats and 100 mg/kg/day in rabbits), cyclosporine oral solution (USP) was teratogenic as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body surface area) are 5,000 and 32,000 times greater, respectively, than the daily recommended human dose of one drop (approximately 28 mcL) of cyclosporine ophthalmic emulsion 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater, respectively, than the daily recommended human dose. An oral dose of 45 mg/kg/day cyclosporine administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. This dose is 7,000 times greater than the daily recommended human dose. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily recommended human dose).

8.2 Lactation

Risk Summary

Cyclosporine is known to appear in human milk following systemic administration, but its presence in human milk following topical treatment has not been investigated. Although blood concentrations are undetectable following topical administration of cyclosporine ophthalmic emulsion *[see Clinical Pharmacology (12.3)]*, caution should be exercised when cyclosporine ophthalmic emulsion is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cyclosporine ophthalmic emulsion and any potential adverse effects on the breast-fed child from cyclosporine.

8.4 Pediatric Use

Safety and efficacy have not been established in pediatric patients below the age of 16.

8.5 Geriatric Use

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

11 DESCRIPTION

Cyclosporine ophthalmic emulsion 0.05% contains a topical calcineurin inhibitor immunosuppressant with anti-inflammatory effects. Cyclosporine's chemical name is

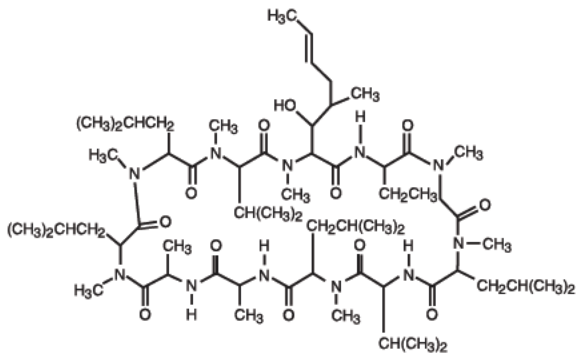
0.187" 0.187"

FRONT SIDE

(b) (4)

Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl] and it has the following structure:

Structural Formula



Formula: $C_{62}H_{111}N_{11}O_{12}$ Mol. Wt.:1202.6

Cyclosporine, USP is a white or almost white powder. Cyclosporine ophthalmic emulsion appears as a white opaque to slightly translucent homogeneous emulsion. It has an osmolality of 230 to 320 mOsmol/kg and a pH of 6.5 to 8.0. Each mL of cyclosporine ophthalmic emulsion contains: **Active:** cyclosporine USP, 0.05%. **Inactives:** anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cyclosporine is an immunosuppressive agent when administered systemically.

In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

12.3 Pharmacokinetics

Blood cyclosporine A concentrations were measured using a specific high pressure liquid chromatography-mass spectrometry assay. Blood concentrations of cyclosporine, in all the samples collected, after topical administration of cyclosporine ophthalmic emulsion 0.05%, twice daily, in humans for up to 12 months, were below the quantitation limit of 0.1 ng/mL. There was no detectable drug accumulation in blood during 12 months of treatment with cyclosporine ophthalmic emulsion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Systemic carcinogenicity studies were conducted in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily recommended human dose of one drop (approximately 28 mcL) of 0.05% cyclosporine ophthalmic emulsion twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis

Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

Impairment of Fertility

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

14 CLINICAL STUDIES

Four multicenter, randomized, adequate and well-controlled clinical studies were performed in approximately 1,200 patients with moderate to severe keratoconjunctivitis sicca. Cyclosporine ophthalmic emulsion demonstrated statistically significant increases in Schirmer wetting of 10 mm versus vehicle at six months in patients whose tear production was presumed to be suppressed due to ocular inflammation. This effect was seen in approximately 15% of cyclosporine ophthalmic emulsion-treated patients versus approximately 5% of vehicle-treated patients. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

No increase in bacterial or fungal ocular infections was reported following administration of cyclosporine ophthalmic emulsion.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cyclosporine ophthalmic emulsion, 0.05% is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine ophthalmic emulsion is also provided in a 60 count carton that must be dispensed intact.

NDC 0378-8760-58
carton of 30 vials

NDC 0378-8760-91
carton of 60 vials

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

Handling the Container

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. Advise patients to not touch the vial tip to their eye to avoid the potential for injury to the eye [*see Warnings and Precautions (5.1)*].

Use with Contact Lenses

Cyclosporine ophthalmic emulsion should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of cyclosporine ophthalmic emulsion [*see Warnings and Precautions (5.2)*].

Administration

Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Mylan®

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in U.S.A.

JANAURY 2022

BACK SIDE

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205894Orig1sS000

LABELING REVIEW(s)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205894Orig1sS000

LABELING REVIEW(s)

***** This document contains proprietary information that cannot be released to the public.***V.25**

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	1/21/2022
ANDA Number(s)	205894
Review Number	5
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	NA
Submission Received Date	1/20/2022
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Burhan Nour

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C5)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received January 20, 2022.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

1.3 POST-APPROVAL REVISIONS (C5)

Not Applicable

2 INSTRUCTIONS FOR ASSESSMENT (C5)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C5)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	1 vial	8/22/2016	Satisfactory
Blister	N/A	N/A		
Carton	Final	30 single-use vials and 60 single-use vials	5/26/2021	Satisfactory
Pouch	Final	1 pouch containing 5 single-use vials	5/26/2021	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final	January 2022	1/20/2022	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C5)

4.1 REGULATORY INFORMATION (C5)

Yes	No	
☐	☒	Are there any applicable issues in DLR's SharePoint Drug Facts ?
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION (C5)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA 050790 / S-027

Supplement Approval Date: 07/18/2017

Proprietary Name: RESTASIS 0.05%

Established Name: cyclosporine ophthalmic emulsion 0.05%

Description of Supplement:

Supplement 027 proposes revision of the package insert to conform to the Pregnancy and Lactation Labeling Rule (PLLR) format, and proposes minor editorial revisions to the RESTASIS MULTIDOSE (cyclosporine ophthalmic emulsion) 0.05% package insert.

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4126070_3699679_090140af8044bd54_NDA050790_2565616

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING
☐ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: **Deficiency Comments:**		

4.3 PATENTS AND EXCLUSIVITIES (C5)

The Orange Book was searched on 1/21/2022.

Table 4 provides Orange Book patents for the Model Labeling (NDA 050790) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
0.05%, 0.05%	9248191	08/27/2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	03/17/2016	None
0.05%, 0.05%	8629111	08/27/2024			IV	01/14/2014	None
0.05%, 0.05%	8633162	08/27/2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	01/22/2014	None
0.05%, 0.05%	8642556	08/27/2024			IV	02/05/2014	None
0.05%, 0.05%	8648048	08/27/2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	02/17/2014	None
0.05%, 0.05%	8685930	08/27/2024			IV	04/02/2014	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C5)

The USP was searched on 01/21/2022.

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: **Deficiency Comments:**		

4.5 MODEL CONTAINER LABELS (C5)

Model container/carton/blister labels (Source: ANRPT-19 received 1/20/2022 and ANRPT-11 received 2/11/2014)

Carton labeling


NDC 0023-9163-30
No. 93346
Restasis®
(Cyclosporine Ophthalmic Emulsion) 0.05%
N
3 0023-9163-30 0
30 Single-Use Vials (0.4 mL each)
Sterile, Preservative-Free
Each mL contains: Active: cyclosporine 0.05% Inactives: glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH.
Usual Dosage: Twice daily approximately 12 hours apart. Invert the vial before using. Use immediately after opening and then discard. Storage: Store at 15°-25°C (59°-77°F). Store vials in the thermoformed tray until use. The entire contents of each tray (30 vials) must be dispensed intact.
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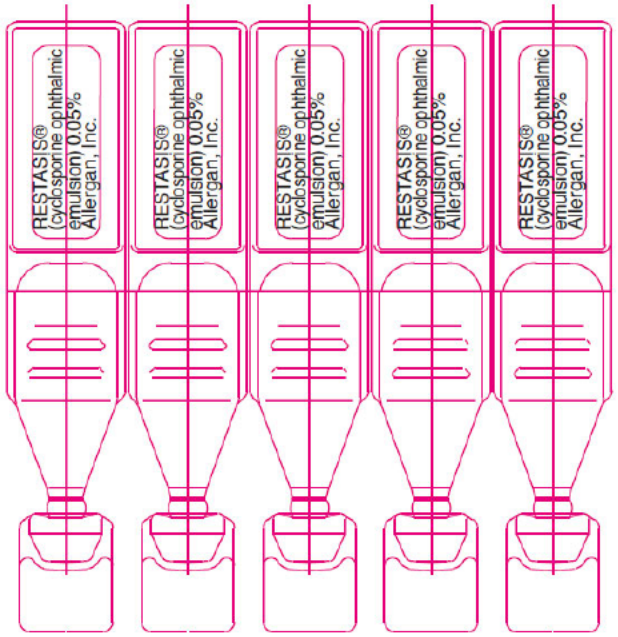
® marks owned by Allergan, Inc.
Patented. See: www.allergan.com/products/patent_notices
Made in Ireland.
54329US11
ALLERGAN
Lot:
Exp.:
Rx only

Vial label



5 ASSESSMENT OF ANDA LABELING AND LABELS (C5)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C5)

5.1.1 DRUG PRODUCT REVIEW (C5)

Previously, the formulation was assessed to be Q1 to the RLD but not Q2 equivalent to the RLD (See drug product in panorama dated 09/29/2020). Since completion of the June 30, 2021 Labeling Review, the applicant's revised drug product formulation has been determined to be acceptable.

5.1.2 DESCRIPTION (C5)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Inactives: glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH.
ANDA Labeling	Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C5)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	RESTASIS® ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 30 or 60 vials are packaged in a polypropylene tray with an aluminum peelable lid. The entire contents of each tray (30 vials or 60 vials) must be dispensed intact. 30 Vials 0.4 mL each - NDC 0023-9163-30 60 Vials 0.4 mL each - NDC 0023-9163-60 Storage: Store at 15°-25 °C (59°-77 °F)

Table 8: Comparison of Model Labeling to ANDA Labeling	
ANDA Labeling	Cyclosporine ophthalmic emulsion, 0.05% is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine ophthalmic emulsion is also provided in a 60 count carton that must be dispensed intact. NDC 0378-8760-58 carton of 30 vials NDC 0378-8760-91 carton of 60 vials Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER(C5)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	(b) (4)
Name and Address on ANDA Container/Carton	Manufactured for: **Mylan Pharmaceuticals Inc.** Morgantown, WV 26505 U.S.A. Made in U.S.A.
Name and Address on ANDA Prescribing Information	Mylan® Manufactured for: **Mylan Pharmaceuticals Inc.** Morgantown, WV 26505 U.S.A. Made in U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.

Deficiency	No Deficiency	
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		OVERALL ASSESSMENT:
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: (b) (4)		

5.2.1 OPHTHALMIC PRODUCTS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Ophthalmic product **cap colors** match the American Academy of Ophthalmology (AAO) packaging color-coding scheme.
☐	☒	Name and quantity (or proportion) of all **inactive ingredients** are listed appropriately.
☐	☒	Tamper evident (ophthalmic products) requirements are met.
Reviewer Comments: **Deficiency Comments:**		

5.3 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments: Acceptable

A DRL was issued on 1/19/2022 for the applicant to revise the structural formula in the DESCRIPTION SECTION, and the HOW SUPPLIED Section of the proposed labeling to be the same as RLD.

Deficiency Comments from C4 addendum:

DESCRIPTION: Revise your structural formula with the same presentation as the reference listed drug (RLD) labeling.

HOW SUPPLIED/STORAGE AND HANDLING

a. Delete 1st paragraph, [redacted] (b) (4) [redacted] ."
b. Revise the 2nd paragraph, first sentence to read, Cyclosporine ophthalmic emulsion, 0.05% is packaged in sterile, preservative-free single-use vials." (replace [redacted] (b) (4) with "packaged" and delete [redacted] (b) (4) ").

Response/Assessment:
Applicant submitted an amendment on 1/21/2022 addressing the above comments
DESCRIPTION
As recommended by the Agency, Mylan has revised our structural formula in the Prescribing Information with the same presentation as that in the reference listed drug (RLD) labeling.
HOW SUPPLIED/STORAGE AND HANDLING
a. As recommended by the Agency, Mylan has revised the Prescribing Information to delete the 1st paragraph under the HOW SUPPLIED/STORAGE AND HANDLING section.
b. As recommended by the Agency, Mylan has revised the 2nd paragraph under the HOW SUPPLIED/STORAGE AND HANDLING section of the Prescribing Information accordingly.
The above changes are acceptable.

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:

Rita Lindie

Digitally signed by Rita Lindie
Date: 1/28/2022 11:30:22AM
GUID: 53c570830001639fca7572eedfad43b0

Burhan Nour

Digitally signed by Burhan Nour
Date: 1/28/2022 11:42:40AM
GUID: 508da70600028ae6e75df33aa0f5b2ce

***** This document contains proprietary information that cannot be released to the public.***V.25**

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	1/12/2022
ANDA Number(s)	205894
Review Number	4 (Addendum)
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	NA
Submission Received Date	05/26/2021
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Burhan Nour

Review Conclusion

☐ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C4)

This review serves as an addendum to the Labeling Review completed on June 30, 2021. This addendum identifies minor labeling deficiencies not previously identified and includes language for communicating these deficiencies to the applicant (see below in section 1.1). This addendum, in identifying minor differences, supersedes any inconsistent statements in the June 30, 2021 review.

This addendum also clarifies one statement in the June 30, 2021 Labeling review. The prior Labeling Review stated: "Previously, the formulation was assessed to be Q1 to the RLD but not Q2 equivalent to the RLD (see drug product in panorama dated 09/29/2020). Applicant has revised the drug product formulation, review is pending." Since completion of the June 30, 2021 Labeling Review, the applicant's revised drug product formulation has been determined to be acceptable.

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)

Labeling Deficiencies determined on January 12, 2022 based on your submission received May 26, 2021.

PRESCRIBING INFORMATION; FULL PRESCRIBING INFORMATION

A. 11 DESCRIPTION: Revise your structural formula with the same presentation as the reference listed drug (RLD) labeling.

B. 16 HOW SUPPLIED/STORAGE AND HANDLING
   i. Delete 1st paragraph, [redacted (b) (4)].
   ii. Revise the 2nd paragraph, first sentence to read, Cyclosporine ophthalmic emulsion, 0.05% is packaged in sterile, preservative-free single-use vials." (replace [redacted (b) (4)] with "packaged" and delete [redacted (b) (4)]").

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)

Not Applicable

1.3 POST-APPROVAL REVISIONS (C4)

Not Applicable

2 INSTRUCTIONS FOR ASSESSMENT (C4)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4)

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	1 vial	5/26/2021	Satisfactory
Blister	N/A	N/A		
Carton	Final	30 single-use vials and 60 single-use vials	5/26/2021	Satisfactory
Pouch	Final	1 pouch containing 5 single-use vials	5/26/2021	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final	10/2018	5/26/2021	Revise
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

Yes	No	
☐	☒	Are there any applicable issues in DLR's SharePoint Drug Facts ?
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION (C4)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original)**: NDA050790 / S-027 **Supplement Approval Date**: 07/18/2017 **Proprietary Name**: RESTASIS 0.05% **Established Name**: cyclosporine ophthalmic emulsion 0.05% **Description of Supplement**: **Supplement 027 proposes revision of the package insert to conform to the Pregnancy and Lactation Labeling Rule (PLLR) format, and proposes minor editorial revisions to the RESTASIS MULTIDOSE (cyclosporine ophthalmic emulsion) 0.05% package insert.** **Link**: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4126070_3699679_090140af8044bd54_NDA050790_2565616
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING
☐ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments:		

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C4)

The Orange Book was searched on 1/12/2022.

Table 4 provides Orange Book patents for the Model Labeling (NDA 050790) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
0.05%, 0.05%	9248191	08/27/2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	03/17/2016	None
0.05%, 0.05%	8629111	08/27/2024			IV	01/14/2014	None
0.05%, 0.05%	8633162	08/27/2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	01/22/2014	None
0.05%, 0.05%	8642556	08/27/2024			IV	02/05/2014	None
0.05%, 0.05%	8648048	08/27/2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	02/17/2014	None
0.05%, 0.05%	8685930	08/27/2024			IV	04/02/2014	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The USP was searched on 01/12/2022.

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

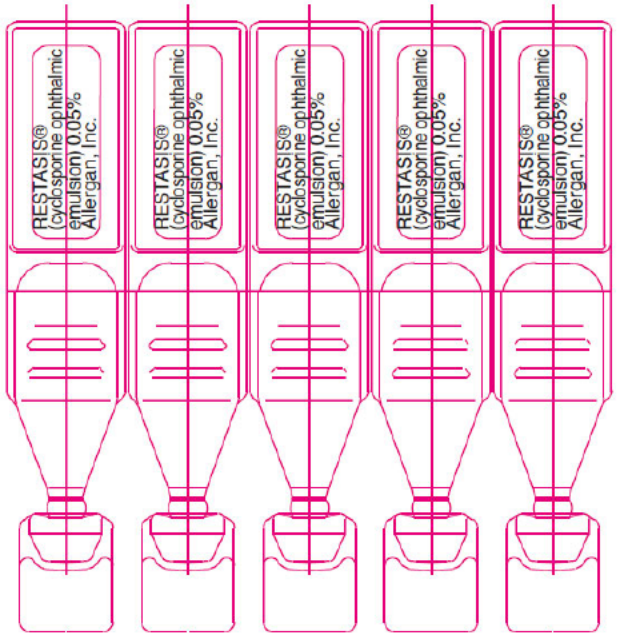
Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: **Deficiency Comments:**		

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: ANRPT-12 received 1/29/2015 and ANRPT-11 received 2/11/2014)

Carton labeling

Vial label



5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Previously, the formulation was assessed to be Q1 to the RLD but not Q2 equivalent to the RLD (see drug product in panorama dated 09/29/2020). Applicant has revised the drug product formulation, review is pending.

5.1.2 DESCRIPTION (C4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Inactives: glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH.
ANDA Labeling	Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	RESTASIS® ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 30 or 60 vials are packaged in a polypropylene tray with an aluminum peelable lid. The entire contents of each tray (30 vials or 60 vials) must be dispensed intact. 30 Vials 0.4 mL each - NDC 0023-9163-30 60 Vials 0.4 mL each - NDC 0023-9163-60

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Storage: Store at 15°-25 °C (59°-77 °F)
ANDA Labeling	Cyclosporine Ophthalmic Emulsion is a sterile white opaque to slightly translucent homogenous emulsion of 0.05% cyclosporine, USP. Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count carton that must be dispensed intact. NDC 0378-8760-58 carton of 30 vials NDC 0378-8760-91 carton of 60 vials Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER(C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	(b) (4)
Name and Address on ANDA Container/Carton	Manufactured for: **Mylan Pharmaceuticals Inc.** Morgantown, WV 26505 U.S.A. Made in U.S.A.
Name and Address on ANDA Prescribing Information	Mylan® Manufactured for: **Mylan Pharmaceuticals Inc.** Morgantown, WV 26505 U.S.A. Made in U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		OVERALL ASSESSMENT:
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: (b) (4)		
Deficiency Comments:		

5.2.1 OPHTHALMIC PRODUCTS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Ophthalmic product **cap colors** match the American Academy of Ophthalmology (AAO) packaging color-coding scheme.

Deficiency	No Deficiency	
☐	☒	Name and quantity (or proportion) of all **inactive ingredients** are listed appropriately.
☐	☒	Tamper evident (ophthalmic products) requirements are met.
Reviewer Comments: **Deficiency Comments:**		

5.3 PRESCRIBING INFORMATION (C4)

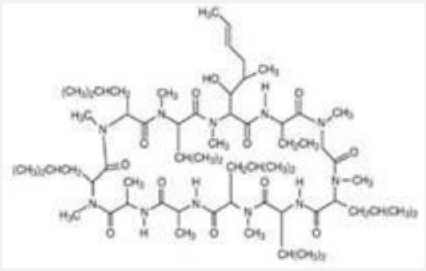
Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		

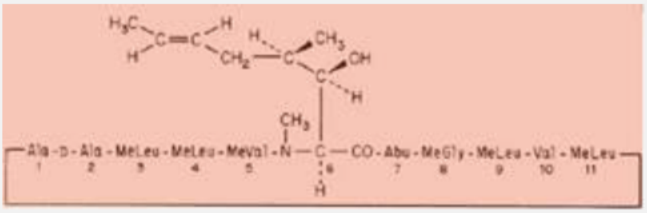
The labeling has been revised by replacing the manufacturer address with "Made in USA". Upon further review, DLR will request that the applicant revised the HOW SUPPLIED Section to be the same as RLD.

Structural formula of ANDA is different from RLD. DLR will request that the applicant revise to be the same as RLD (see below).

RLD



ANDA



Deficiency Comments:

DESCRIPTION: Revise your structural formula with the same presentation as the reference listed drug (RLD) labeling.
HOW SUPPLIED/STORAGE AND HANDLING
a. Delete 1st paragraph, [redacted] (b) (4) [redacted]."
b. Revise the 2nd paragraph, first sentence to read, Cyclosporine ophthalmic emulsion, 0.05% is packaged in sterile, preservative-free single-use vials." (replace [redacted] (b) (4) " with "packaged" and delete [redacted] (b) (4)

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)
Reviewer Comments: **Deficiency Comments**:

Rita Lindie

Digitally signed by Rita Lindie
Date: 1/19/2022 09:22:40AM
GUID: 53c570830001639fca7572eedfad43b0

Burhan Nour

Digitally signed by Burhan Nour
Date: 1/19/2022 09:36:24AM
GUID: 508da70600028ae6e75df33aa0f5b2ce

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	06/14/2021
ANDA Number(s)	205894, ORIG-1
Review Number	4
Applicant Name	Mylan Pharmaceuticals Inc., a Viatris Company
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	NA
Submission Received Date	05/26/2021
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Florence Marshall

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C4)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received 05/26/2021.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C4)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C4)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

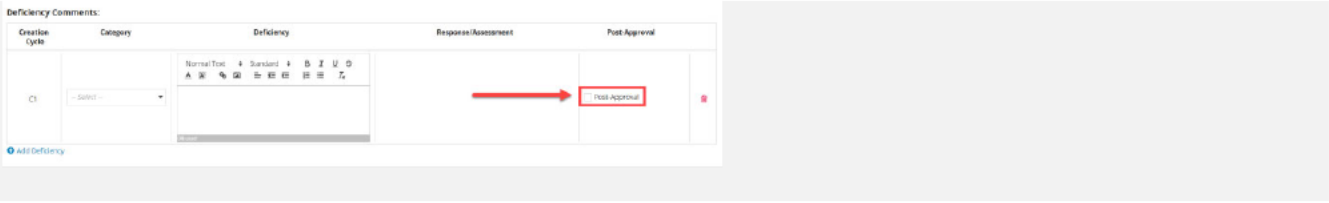
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 vial	5/26/2021	Satisfactory
Blister	N/A	N/A		
Carton	Final	30 single-use vials and 60 single-use vials	5/26/2021	Satisfactory
Pouch	Final	1 pouch containing 5 single-use vials	5/26/2021	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	10/2018	5/26/2021	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? **Controlled Correspondence Summary – 1603141** Controlled Correspondence was filed on September 28, 2015 by Dr. Reddy's Laboratories, Inc. *The firm intended to submit an ANDA for Cyclosporine Ophthalmic Emulsion 0.05% which will be a generic version of Restasis (cyclosporine ophthalmic emulsion) 0.05% marketed by Allergan, Inc. (NDA# 050790). The RLD drug product was packaged in sterile vial which contains 0.4mL fill in 0.9mL LDPE vial. Dr. Reddy intended to affix a transparent sticker/label on both sides of the stem of the LDPE vial with similar information as the RLD.* *The firm proposed to conduct appropriate extractable/leachable studies along with the sticker labels to evaluate the quality of the final product. Images of reference listed drug product and proposed generic product was listed for agency used. The proposed generic product was considered acceptable when the reference product printed the information on the stem of the vial.* *The Office of Generic Drug, Division of Labeling Review's policy required that firm review the product information on container of Cyclosporine Ophthalmic Emulsion 0.05% and proposed to use a sticker/label to print information similar with the RLD acceptable.*
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint?

4.2 MODEL PRESCRIBING INFORMATION (C4)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** NDA050790 / S-027 **Supplement Approval Date:** 07/18/2017 **Proprietary Name:** RESTASIS 0.05% **Established Name:** cyclosporine ophthalmic emulsion 0.05% **Description of Supplement:** **Supplement 027 proposes revision of the package insert to conform to the Pregnancy and Lactation Labeling Rule (PLLR) format, and proposes minor editorial revisions to the RESTASIS MULTIDOSE (cyclosporine ophthalmic emulsion) 0.05% package insert.** **Link:** https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4126070_3699679_090140af8044bd54_NDA050790_2565616
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING
☐ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: **Deficiency Comments:**		

4.3 PATENTS AND EXCLUSIVITIES (C4)

The Orange Book was searched on 06/14/2021

Table 4 provides Orange Book patents for the Model Labeling (NDA050790) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
0.05%, 0.05%	9248191	08/27/2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	03/17/2016	None
0.05%, 0.05%	8629111	08/27/2024			IV	01/14/2014	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter Carve-out or None)**
0.05%, 0.05%	8633162	08/27/2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	01/22/2014	None
0.05%, 0.05%	8642556	08/27/2024			IV	02/05/2014	None
0.05%, 0.05%	8648048	08/27/2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	IV	02/17/2014	None
0.05%, 0.05%	8685930	08/27/2024			IV	04/02/2014	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The USP was searched on 06/14/2021

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

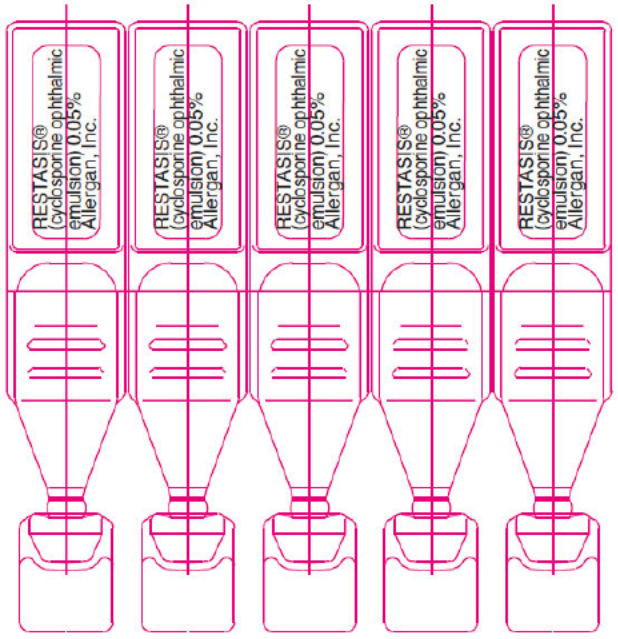
Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
		USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: **Deficiency Comments:**		

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: ANRPT-12 received 1/29/2015 and ANRPT-11 received 2/11/2014)

Carton labeling

Vial label



5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Previously, the formulation was assessed to be Q1 to the RLD but not Q2 equivalent to the RLD (see drug product in panorama dated 09/29/2020). Applicant has revised the drug product formulation, review is pending.

5.1.2 DESCRIPTION (C4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Inactives: glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH.
ANDA Labeling	Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	RESTASIS® ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 30 or 60 vials are packaged in a polypropylene tray with an aluminum peelable lid. The entire contents of each tray (30 vials or 60 vials) must be dispensed intact. 30 Vials 0.4 mL each - NDC 0023-9163-30 60 Vials 0.4 mL each - NDC 0023-9163-60

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Storage: Store at 15°-25 °C (59°-77 °F)
ANDA Labeling	Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count carton that must be dispensed intact. NDC 0378-8760-58 carton of 30 vials NDC 0378-8760-91 carton of 60 vials Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER(C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	(b) (4)
Name and Address on ANDA Container/Carton	Manufactured for: **Mylan Pharmaceuticals Inc.** Morgantown, WV 26505 U.S.A. Made in U.S.A.
Name and Address on ANDA Prescribing Information	Mylan® Manufactured for: **Mylan Pharmaceuticals Inc.** Morgantown, WV 26505 U.S.A. Made in U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		

Deficiency	No Deficiency	
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
	THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:	
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: (b) (4)		
Deficiency Comments:		

5.2.1 OPHTHALMIC PRODUCTS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Ophthalmic product **cap colors** match the American Academy of Ophthalmology (AAO) packaging color-coding scheme.
☐	☒	Name and quantity (or proportion) of all **inactive ingredients** are listed appropriately.
☐	☒	Tamper evident (ophthalmic products) requirements are met.
Reviewer Comments:		

Deficiency Comments:

5.3 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The labeling has been revised by replacing the manufacturer address with "Made in USA".

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:

Rita Lindie

Digitally signed by Rita Lindie
Date: 6/17/2021 08:34:50AM
GUID: 53c570830001639fca7572eedfad43b0

Marshall Florence

Digitally signed by Marshall Florence
Date: 6/30/2021 11:46:51AM
GUID: 55eefa420051b501ac3ced124279f785

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	8/16/2017
ANDA Number(s)	205894
Review Number	3
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s)	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	None
Submission Received Date	8/11/2017
Labeling Reviewer	Rita Lindie
Acting Labeling Team Leader	Theresa Liu

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) dated (add date):

1. GENERAL COMMENTS
   Comment

2. CONTAINER LABEL
   a. Comment
   b. Comment
3. CARTON LABELING
4. PRESCRIBING INFORMATION
   a. Comment
   b. Subheading
      i. Comment
      ii. Comment
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Choose an item. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
NA to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

11/1/2013-Original ANDA was received.

7/10/2015-Amendment was submitted.

8/9/2016-ECD was issued.

8/22/2016-Applicant submitted response to ECD.

C2 was satisfactory as of 8/31/2016. There were no post approval comments,

From 8/11/2017 cover letter

Mylan wishes to amend the application to provide labeling that has been revised pursuant to the CDER Internet Posting dated July 18, 2017 (NDA 050790/S-027) which contained approved labeling revisions for the Reference Listed Drug (RLD), RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% (Allergen, Inc.). In accordance with 21 CFR §314.96(d)(2), Mylan confirms that any changes described in this amendment do not require a patent certification pursuant to 21 CFR §314.96(d)(1).

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

Container, pouch and carton labeling were found to be acceptable in C2 review.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

It is noted that the RLD was originally assigned NDA 021023. It was administratively closed and reassigned NDA 050790 because it's an antibiotic submitted under 505(b) after 11/21/97, to which section 125 exemptions apply.

The original insert labeling approved 12/23/02, the product is packaged with 32 vials per tray configuration, as stated in the HOW SUPPLIED section. There was also a 8 count physical sample packaged in cartons.

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs, CMC Review #1 dated 5/21/99.

(b) (4)

(b) (4)

Question to chemist

The NDA RLD uses a " (b) (4) to prevent water loss. Please confirm the acceptability of the secondary packaging (aluminum pouch) for this ANDA.

Chemist response

(b) (4)

However, we have several ANDAs for Cyclosporine, all with different secondary packaging to RLD, we will standardize the review language in response to your labeling issue.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

CP	ITDA-2017-P-4745	Restasis	cyclosporine ophthalmic emulsion; 0.5%	Allergan requests that FDA refuse to approve any pending ANDA for cyclosporine ophthalmic emulsion for which RESTASIS® is the RLD that relies on in vitro or other nonclinical analyses, and does not rely on one or more appropriately designed clinical endpoint bioequivalence studies, as previously suggested by FDA.	050790	No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead	Disciplines can send IR/ECD/ No CC without contacting Policy Lead
Patent/Exclusivity	Internal	Restasis	cyclosporine ophthalmic emulsion; 0.5%	Patent/Exclusivity issues are being reviewed	050790	No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead	All disciplines can send communications (IR/ECD/CC)

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 050790/S-027 **Supplement Approval Date:** 7/18/2017 **Proprietary Name:** Restasis **Established Name:** Cyclosporine Ophthalmic Emulsion, 0.05% **Description of Supplement:** Supplement 027 proposes revision of the package insert to conform to the Pregnancy and Lactation Labeling Rule (PLLR) format, and proposes minor editorial revisions to the RESTASIS MULTIDOSE (cyclosporine ophthalmic emulsion) 0.05% package insert.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** NA to enter text. **Supplement Approval Date:** NA to enter text. **Proprietary Name:** NA to enter text. **Established Name:** NA to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** NA to enter text.
☐ **OTHER (Describe):** NA to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

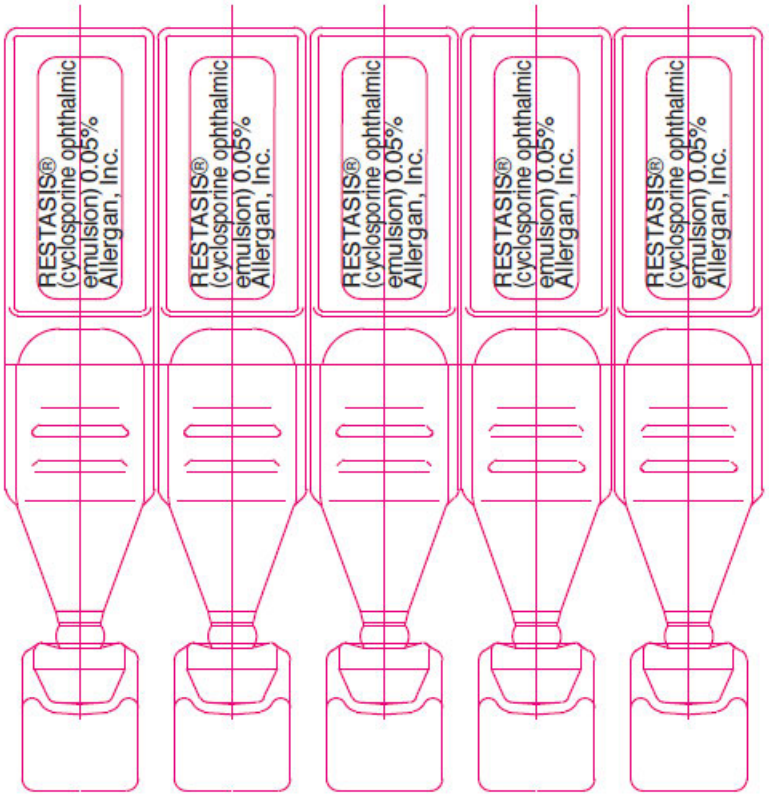
Reviewer Comments: Acceptable

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-12 received 1/29/2015 & ANRPT-11 received 2/11/2014]

Carton labeling

Vial label



3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	**Monograph ? YES or NO**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
USP	8/16/2017	No	NA to enter text.	NA to enter text.
PF	8/16/2017	No	NA to enter text.	NA to enter text.

Reviewer Comments:

NA to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 8/31/2016.

Table 3 provides Orange Book patents for the Model Labeling NDA 050790 **NA to enter NDA number** and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter "Carve-out" or "None")**
8629111	Aug 27, 2024			PIV	1/15/2014	None
8633162	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	1/23/2014	None
8642556	Aug 27, 2024			PIV	2/6/2014	None
8648048	Aug 27, 2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	2/18/2014	None
8685930	Aug 27, 2024			PIV	4/3/2014	None
9248191	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	3/18/2016	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter "Carve-out" or "None")**
NA to enter text.					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

NA to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.	Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.	No changes

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
Cyclosporine Ophthalmic Emulsion is a sterile white opaque to slightly translucent homogenous emulsion of 0.05% cyclosporine, USP. Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count (2 x 30) carton that must be dispensed intact. NDC 0378-8760-58 carton of 30 vials NDC 0378-8760-91 carton of 60 vials Store at 15° to 25°C (59° to 77°F). [See USP Controlled Room Temperature.]	Cyclosporine Ophthalmic Emulsion is a sterile white opaque to slightly translucent homogenous emulsion of 0.05% cyclosporine, USP. Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count (2 x 30) carton that must be dispensed intact. NDC 0378-8760-58 carton of 30 vials NDC 0378-8760-91 carton of 60 vials Store at 20º to 25ºC (68º to 77ºF). [See USP Controlled Room Temperature.]	No changes

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment

Table 7: Manufacturer/Distributor/Packer Statements
(b) (4)

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 vial	8/22/2016	Satisfactory
Blister	NA	NA to enter text.	NA to enter text.	NA to enter text.
Carton	Final	30 single-use vials and 60 single-use vials	8/22/2016	Satisfactory
(Other – specify)- Pouch	Final	1 pouch container a 5 vials	8/22/2016	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	8/2017	8/11/2017	Satisfactory
Medication Guide	NA	NA to enter text.	NA to enter text.	NA to enter text.
Patient Information	NA	NA to enter text.	NA to enter text.	NA to enter text.
SPL Data Elements		8/2016	8/22/2016	Satisfactory

Rita Lindie

Digitally signed by Rita Lindie
Date: 8/16/2017 02:35:32PM
GUID: 53c570830001639fca7572eedfad43b0

Theresa Liu

Digitally signed by Theresa Liu
Date: 8/17/2017 10:31:11AM
GUID: 508da70a00028d58911de18a598cda6f

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	8/31/2016
ANDA Number(s)	205894
Review Number	2
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s)	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	None
Submission Received Date	8/22/2016
Labeling Reviewer	Rita Lindie
Acting Labeling Team Leader	Theresa Liu

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) dated (add date):

1. GENERAL COMMENTS
   Comment

2. CONTAINER LABEL
   a. Comment
   b. Comment
3. CARTON LABELING
4. PRESCRIBING INFORMATION
   a. Comment
   b. Subheading
      i. Comment
      ii. Comment
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Choose an item. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
NA to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

11/1/2013-Original ANDA was received.

7/10/2015-Amendment was submitted.

8/9/2016-ECD was issued.

8/22/2016-Applicant submitted response to ECD.

Mylan's responses to the specific comments in the Agency's Easily Correctable Labeling Deficiency Correspondence dated August 9, 2016 are as follows:

LABELING:

1. GENERAL COMMENTS

FDA COMMENT

a. The Orange Book has been updated with new patent information associated with NDA 050790 (Patent No. 9248191). Please address this patent.

MYLAN RESPONSE

Mylan wishes to inform the Agency that the Patent Amendment addressing U.S. Patent No. 9,248,191 was submitted on March 18, 2016 (Sequence No. 0020).

2. CONTAINER LABEL

FDA COMMENT

a. Revise the established name to include "Tall Man" lettering on the container and/or carton labeling. Refer to http://www.fda.gov/drugs/drugsafety/medicationerrors/ucm164587.htm

MYLAN RESPONSE

As recommended by the Agency, the established name has been revised to read as "CycloSPORINE Injection". The revised container label is provided in Section 1.14.2.1 (Final Carton and/or Container Label).

3. POUCH LABELING

FDA COMMENT

a. See applicable container label comments.

MYLAN RESPONSE

As recommended by the Agency, the Pouch labeling has been revised to include the established name "CycloSPORINE Injection". The revised label is provided in Section 1.14.2.1 (Final Carton and/or Container Label).

FDA COMMENT

b. Add a linear bar code to the label per 21 CFR 201.25(c).

MYLAN RESPONSE

As recommended by the Agency, a linear bar code has been included on the pouch label. The revised label is provided in Section 1.14.2.1 (Final Carton and/or Container Label).

FDA COMMENT

c. We recommend using the standard USP Controlled Room Temperature statement. Revise the storage statement to read "Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]."

MYLAN RESPONSE

As recommended by the Agency, the storage statement has been revised to read as "Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]". The revised label is provided in Section 1.14.2.1 (Final Carton and/or Container Label).

FDA COMMENT

d. Revise statement "FOR USE IN THE EYES ONLY" to "FOR USE IN THE EYES"

MYLAN RESPONSE

As recommended by the Agency, the statement has been revised to read as "FOR USE IN THE EYES". The revised label is provided in Section 1.14.2.1 (Final Carton and/or Container Label).

4. CARTON LABELING (30 Single-use Vials)

FDA COMMENT

a. See applicable container label and pouch labeling comments.

MYLAN RESPONSE

As requested by the Agency, the carton labeling has been revised accordingly. The revised label is provided in Section 1.14.2.1 (Final Carton and/or Container Label).

5. CARTON LABELING (60 Single-use Vials)

FDA COMMENT

a. See applicable container label and pouch labeling comments.

MYLAN RESPONSE

As requested by the Agency, the carton labeling has been revised accordingly. The revised label is provided in Section 1.14.2.1 (Final Carton and/or Container Label).

FDA COMMENT

b. Delete [redacted] (b) (4) from principal display panel and back panel.

MYLAN RESPONSE

As requested by the Agency, the statement [redacted] (b) (4) has been deleted from the principal display panel and back panel. The revised label is provided in Section 1.14.2.1 (Final Carton and/or Container Label).

6. PRESCRIBING INFORMATION

FDA COMMENT

a. See applicable pouch labeling comments.

MYLAN RESPONSE

As requested by the Agency, the package insert has been revised accordingly. The final package insert is provided in Section 1.14.2.2 (Final Package Insert).

FDA COMMENT

b. HIGHLIGHTS, limitation statement: Revise the presentation of the established name to appear in upper case letters as such: "These highlights do not include all the information needed to use CYCLOSPORINE OPHTHALMIC EMULSION safely and effectively. See full prescribing information for CYCLOSPORINE OPHTHALMIC EMULSION."

MYLAN RESPONSE

As requested by the Agency the established name in Highlights, limitation statement has been revised to appear in upper case letters. The final package insert is provided in Section 1.14.2.2 (Final Package Insert).

FDA COMMENT

c. Please revise the established name located above the "Initial U.S. Approval" to "CYCLOSPORINE ophthalmic emulsion"

Page 4 of 5

MYLAN RESPONSE

As requested by the Agency, the established name has been revised to read as "CYCLOSPORINE ophthalmic emulsion". The final package insert is provided in Section 1.14.2.2 (Final Package Insert).

Applicant addressed all of the above comments.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

Container, pouch and carton labeling were updated as requested. Changes are acceptable.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

It is noted that the RLD was originally assigned NDA 021023. It was administratively closed and reassigned NDA 050790 because it's an antibiotic submitted under 505(b) after 11/21/97, to which section 125 exemptions apply.

The original insert labeling approved 12/23/02, the product is packaged with 32 vials per tray configuration, as stated in the HOW SUPPLIED section. There was also a 8 count physical sample packaged in cartons.

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs, CMC Review #1 dated 5/21/99.

(b) (4)

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

Patent/Exclusivity	Internal	Restasis	cyclosporine ophthalmic emulsion; 0.5%	Patent/Exclusivity issues are being reviewed	050790	No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead	All disciplines can send communications (IR/ECD/CC)

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒**MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): 050790/S-021

Supplement Approval Date: 5/31/2013

Proprietary Name: Restasis

Established Name: Cyclosporine Ophthalmic Emulsion, 0.05%

Description of Supplement:

This "Prior Approval" supplemental new drug application provides for the addition of a 60 count secondary package for RESTASIS (which would be an alternate configuration to the currently approved 30 count secondary packaging) and for associated changes to the labeling.

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** NA to enter text. **Supplement Approval Date:** NA to enter text. **Proprietary Name:** NA to enter text. **Established Name:** NA to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** NA to enter text.
☐ **OTHER (Describe):** NA to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

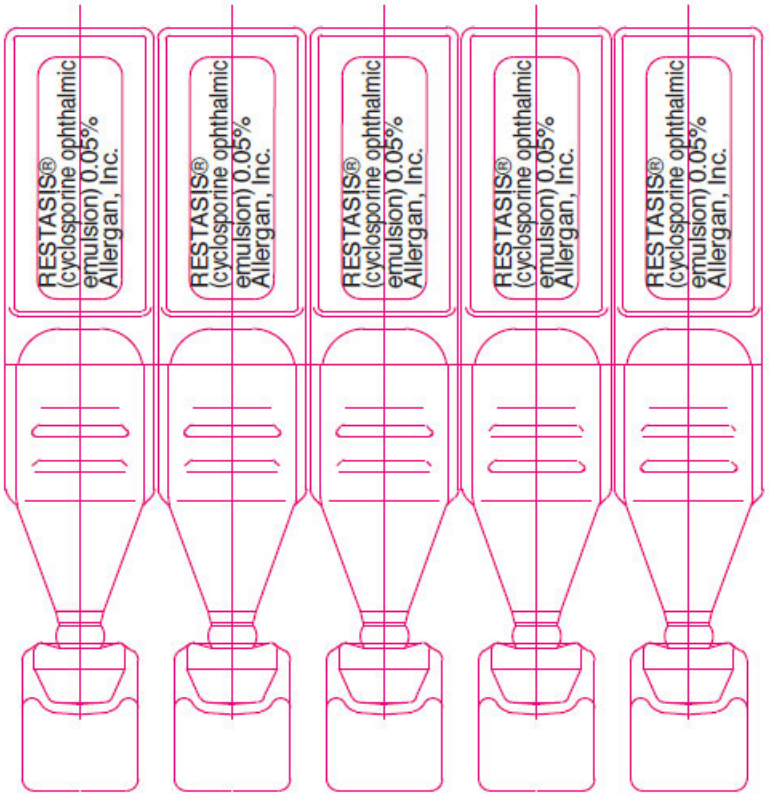
Reviewer Comments: Acceptable

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-12 received 1/29/2015 & ANRPT-11 received 2/11/2014]

Carton labeling

Vial label



TAMPO PRINT FOR
ROMMELAG 2953Q (WESTPORT)

0145001

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	8/31/2016	No	NA to enter text.	NA to enter text.
PF	8/31/2016	No	NA to enter text.	NA to enter text.

Reviewer Comments:

NA to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 8/31/2016.

Table 3 provides Orange Book patents for the Model Labeling **NA to enter NDA number** and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
8629111	Aug 27, 2024			PIV	1/15/2014	None
8633162	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	1/23/2014	None
8642556	Aug 27, 2024			PIV	2/6/2014	None
8648048	Aug 27, 2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	2/18/2014	None
8685930	Aug 27, 2024			PIV	4/3/2014	None
9248191	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	3/18/2016	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Applicant addressed patent, 9248191.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter "Carve-out" or "None")**
NA to enter text.					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

NA to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.	Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.	No changes

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
(b) (4)	Cyclosporine Ophthalmic Emulsion is a sterile white opaque to slightly translucent homogenous emulsion of 0.05% cyclosporine, USP. Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count (2 x 30) carton that must be dispensed intact. NDC 0378-8760-58 carton of 30 vials NDC 0378-8760-91 carton of 60 vials Store at 20º to 25ºC (68º to 77ºF). [See USP Controlled Room Temperature.]	Updated to include statement, "[See USP Controlled Room Temperature.]

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. (b) (4)	Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A.	No changes

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

Issue created on 3/4/2016 for CMC regarding the acceptability of the secondary packaging (aluminum pouch) for this ANDA. Issue is still pending. Email generated to CMC reviewer.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 vial	8/22/2016	Satisfactory
Blister	NA	NA to enter text.	NA to enter text.	NA to enter text.
Carton	Final	30 single-use vials and 60 single-use vials	8/22/2016	Satisfactory
(Other – specify)- Pouch	Final	1 pouch container a 5 vials	8/22/2016	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	8/2016	8/22/2016	Satisfactory
Medication Guide	NA	NA to enter text.	NA to enter text.	NA to enter text.
Patient Information	NA	NA to enter text.	NA to enter text.	NA to enter text.
SPL Data Elements		8/2016	8/22/2016	Satisfactory

Theresa Liu

Digitally signed by Theresa Liu
Date: 9/02/2016 10:37:31AM
GUID: 508da70a00028d58911de18a598cda6f

Rita Lindie

Digitally signed by Rita Lindie
Date: 8/31/2016 02:09:48PM
GUID: 53c570830001639fca7572eedfad43b0

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	2/29/2016
ANDA Number(s)	205894
Review Number	1
Applicant Name	Mylan Pharmaceuticals Inc.
Established Name & Strength(s)	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	NA
Submission Received Date	11/1/2013, 7/10/2015
Labeling Reviewer	Rita Lindie
Acting Labeling Team Leader	Theresa Liu

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on March 4, 2016 based on your submissions dated November 1, 2013 and July 10, 2015.

1. GENERAL COMMENTS
    a. The Orange Book has been updated with new patent information associated with NDA 050790 (Patent No. 9248191). Please address this patent.

2. CONTAINER LABEL
    a. Revise the established name to include "Tall Man" lettering on the container and/or carton labeling. Refer to http://www.fda.gov/drugs/drugsafety/medicationerrors/ucm164587.htm

3. POUCH LABELING
    a. See applicable container label comments.
    b. Add a linear bar code to the label per 21 CFR 201.25(c).
    c. We recommend using the standard USP Controlled Room Temperature statement. Revise the storage statement to read "Store at 20º to 25ºC (68º to 77ºF) [See USP Controlled Room Temperature]."
    d. Revise statement [redacted (b) (4)]" to "FOR USE IN THE EYES"

4. CARTON LABELING (30 Single-use Vials)
    a. See applicable container label and pouch labeling comments.

5. CARTON LABELING (60 Single-use Vials)
    a. See applicable container label and pouch labeling comments.
    b. Delete [redacted (b) (4)] from principal display panel and back panel.

6. PRESCRIBING INFORMATION
    a. See applicable pouch labeling comments.
    b. HIGHLIGHTS, limitation statement: Revise the presentation of the established name to appear in upper case letters as such: "These highlights do not include all the information needed to use CYCLOSPORINE OPHTHALMIC EMULSION safely and effectively. See full prescribing information for CYCLOSPORINE OPHTHALMIC EMULSION."
    c. Please revise the established name located above the "Initial U.S. Approval" to "CYCLOSPORINE ophthalmic emulsion"

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date).

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

NA to enter text.

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES
Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if original):** 050790/S-021 **Supplement Approval Date:** 5/31/2013 **Proprietary Name:** Restasis **Established Name:** Cyclosporine Ophthalmic Emulsion, 0.05% **Description of Supplement:** This "Prior Approval" supplemental new drug application provides for the addition of a 60 count secondary package for RESTASIS (which would be an alternate configuration to the currently approved 30 count secondary packaging) and for associated changes to the labeling.

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ MOST RECENTLY APPROVED ANDA RLD LABELING **ANDA#/Supplement# (S-000 if original):** NA to enter text. **Supplement Approval Date:** NA to enter text. **Proprietary Name:** NA to enter text. **Established Name:** NA to enter text. **Description of Supplement:** NA to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** NA to enter text.
☐ **OTHER (Describe):** NA to enter text.

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: ANRPT-12 received 1/29/2015 & ANRPT-11 received 2/11/2014)

Carton label

Vial label

2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	2/29/2016	No	NA to enter text.	NA to enter text.
PF	2/29/2016	No	NA to enter text.	NA to enter text.

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/29/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.
(For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
8629111	Aug 27, 2024			PIV	1/15/2014	None
8633162	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	1/23/2014	None
8642556	Aug 27, 2024			PIV	2/6/2014	None
8648048	Aug 27, 2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	2/18/2014	None
8685930	Aug 27, 2024			PIV	4/3/2014	None
9248191	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	Not addressed		

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA to enter text.					

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufactured (Cite Source)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
(b) (4)		

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Is the established name for this ANDA acceptable? **YES**
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Are the required USP recommendations reflected in the labeling? **NA**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **YES**

Reviewer Comments:

The model labeling for NDA 050790 is associated with the following packaging configurations:
30 Vials 0.4 mL each and 60 Vials 0.4 mL each

The firm is proposing the same for ANDA 205894.

Comments to firm:
-The Orange Book has been updated with new patent information associated with NDA 050790 (Patent No. 9248191). Please address this patent.
- HIGHLIGHTS, limitation statement: Revise the presentation of the established name to appear in upper case letters as such: "These highlights do not include all the information needed to use CYCLOSPORINE OPHTHALMIC EMULSION safely and effectively. See full prescribing information for CYCLOSPORINE OPHTHALMIC EMULSION."
-Please revise the established name located above the "Initial U.S. Approval" to "CYCLOSPORINE ophthalmic emulsion"

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
Inactives: glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH.	Inactives: anhydrous glycerin, carbomer copolymer type A, castor oil, polysorbate 80, water for injection, and sodium hydroxide to adjust pH.

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling Memorandum of Understanding (MOU)?
NO

(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **YES**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:
From 3.2.P.1

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	RESTASIS® ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 30 or 60 vials are packaged in a polypropylene tray with an aluminum peelable lid. The entire contents of each tray (30 vials or 60 vials) must be dispensed intact. 30 Vials 0.4 mL each - NDC 0023-9163-30 60 Vials 0.4 mL each - NDC 0023-9163-60 Storage: Store at 15-25°C (59-77°F).
ANDA Labeling	(b) (4)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **NO**
If the chemistry review does NOT follow the MOU, is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NA**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **NO**

Reviewer Comments:
Comments to firm:
- Revise the storage statement to read "Store at 20º to 25ºC (68º to 77ºF) [See USP Controlled Room Temperature]."

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **NA**
Is the Medication Guide same as the model labeling, except for allowable differences? **NA**
Does the Medication Guide meet the requirements of 21 CFR 208.20? **NA**
Has the Applicant committed to provide a sufficient number of medication guides? **NA**
Is the phonetic spelling of the proprietary or established name present? **NA**
Is FDA 1-800-FDA-1088 phone number included? **NA**

Reviewer Comments:
NA to enter text.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **NA**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:
NA to enter text.

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NO**
Is container label too small to contain all required information? **YES** If yes, does the container meet the "too small" exemption found in 21 CFR 201.10(i)? **YES**

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**

Is the following information properly displayed?

- Net quantity statement: **NA**
- Route(s) of administration (other than oral): **YES**
- Warnings (if any) or cautionary statements (if any): **NA**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **NA**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **NA**
- Product strength equivalency statement: **NA**
- NDC: **NA**
- Bar code per 21 CFR 201.25(c)(2): **NO**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NO**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments:
The container label is too small to contain all required information. The container label does meet the "too small" exemption. It does contain the minimum amount of required information, i.e. established name, lot number and name of manufacturer.

Comments to firm
- Revise the established name to include "Tall Man" lettering on the container and/or carton labeling. Refer to http://www.fda.gov/drugs/drugsafety/medicationerrors/ucm164587.htm

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
NA to enter text.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
NA to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
NA to enter text.

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **NA**

Reviewer Comments:
NA to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **YES** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **YES**
If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Reviewer Comments:
Five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. It is also provided in a 60 count carton.

Comments to firm
-See applicable container label comments.
-Add a linear bar code to the label per 21 CFR 201.25(c).
-Revise statement [redacted] (b) (4) " to "FOR USE IN THE EYES"

Carton containing 60 single-use vials
-Delete [redacted] (b) (4) from PDP and back panel.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? **NA**
Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the established name for this ANDA acceptable? **NA**
Is title case used in expressing the established name? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **NA**
Is the following information properly displayed?
Pharmacological category: **NA**
Net quantity statement: **NA**
Route(s) of administration (other than oral): **NA**

Warnings (if any) or cautionary statements (if any): **NA**
NDC: **NA**
Bar code per 21 CFR 201.25(c)(2): **NA**

Is the Manufacturer/Distributor/Packager statement acceptable? **NA**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected in the labeling? **NA**
Is the storage statement acceptable? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**

Reviewer Comments:
NA to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Inactive Ingredients**
NA to enter text.	NA to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **NA**
Are the inactive ingredients listed in alphabetical order? **NA**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:
NA to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	NA to enter text.
ANDA (enter source of information of product description on the right hand column; e.g., chemistry Review & date, Module 3.2.P.5.1)	NA to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **NA**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **NA**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **NA**

Reviewer Comments:
NA to enter text.

3.2.2 OTC: OTHER PATIENT LABELING

Are other patient labeling required? **NA**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was other patient labeling submitted? **NA**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:
NA to enter text.

3.3 CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **NO**
Are the tamper evident requirements met for OTC and Controlled Substances? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **NA**

For ophthalmic products:
Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:
Is there text on the cap/ferrule overseal of this injectable product? **NA**
If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap and ferrule color? **NA to enter text.**
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**
If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
NA to enter text.	NA to enter text.	NA to enter text.

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **NA**
Are the stated contents in the table above acceptable? **NA**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **NA**
Are the labeling requirements met per 21 CFR 201.323? **NA**

Reviewer Comments:
NA to enter text.

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (Cite source of information such as the chemistry review that follows the MOU, Product Specification in 3.2.P.5.1, Commercial Batch Record in 3.2.P.3.3. etc.)**
NA to enter text.	NA to enter text.	NA to enter text.
NA to enter text.	NA to enter text.	NA to enter text.

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments: Acceptable

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:
The NDA RLD uses a "thermoformed tray" to prevent water loss. Please confirm the acceptability of the secondary packaging (aluminum pouch) for this ANDA.

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

Reviewer Comments:
NA to enter text.

6. SPECIAL CONSIDERATIONS

It is noted that the RLD was originally assigned NDA 021023. It was administratively closed and reassigned NDA 050790 because it's an antibiotic submitted under 505(b) after 11/21/97, to which section 125 exemptions apply.

The original insert labeling approved 12/23/02, the product is packaged with (b) (4) vials per tray configuration, as stated in the HOW SUPPLIED section. There was also a (b) (4) physical sample packaged in cartons.

Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs, CMC Review #1 dated 5/21/99

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	1 vial	7/10/2015	Revise
Blister	NA	NA to enter text.	NA to enter text.	NA to enter text.
Carton	Draft	30 single-use vials and 60 single-use vials	7/10/2015	Revise
(Other – specify) Pouch	Draft	1 pouch container a 5 vials	7/10/2015	Revise
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**

Prescribing Information	Draft	JUNE 2013 CAT:CYOP:RX	7/10/2015	Revise
Medication Guide	NA	NA to enter text.	NA to enter text.	NA to enter text.
Patient Information	NA	NA to enter text.	NA to enter text.	NA to enter text.
SPL Data Elements	NA to enter text.	June 2013	7/10/2015	Satisfactory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205894Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: CMC Adequate

☒ **Approval**
☐ **Information Request _____days for applicant to respond if issued by _____), OR**
☐ **Complete Response – Minor**
☐ **Complete Response – Major**

Elemental Impurities: Comply with the USP <232/233> requirements or ICH Q3D recommendations:
☒ Yes
☐ No

Compliance with USP monographs:

- Drug Substance(s): ☒Yes; ☐No; ☐NA
- Drug Product: ☐Yes; ☐Yes*, with Differ Statement; ☐No; ☒NA

***If checked, please include the Differ Statement(s) here:**

Any approved comparability protocol: ☐Yes, How Many ____ ☒No

ANDA 205894
Drug Product Review #4

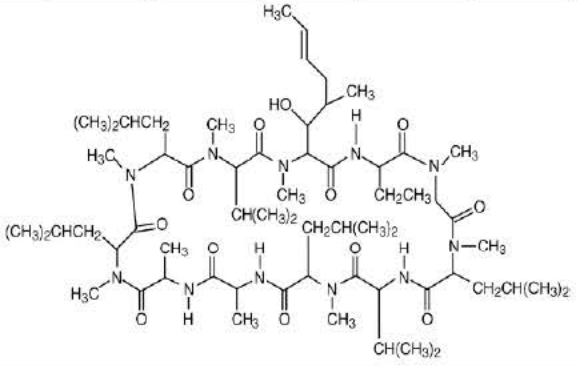
Drug Name/Dosage Form	**Cyclosporine Ophthalmic Emulsion**
Strength	0.05%
Reviewer(s)	**Asif Rasheed, CDER/OPQ/OLDP/DLBP I**
Applicant	**Mylan Pharmaceuticals Inc.**

SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Date of the Submission
eCTD 0045 – Response to CRL	12/17/2020
eCTD 0051 – Unsolicited Amendment	05/26/2021
eCTD 0052 – Response to Information Request	07/15/2021
eCTD 0053 – Response to Information Request	07/26/2021
eCTD 0054 – Response to Information Request	11/01/2021

The submissions eCTD 0044, 0046, 0047, 0048, 0049, 0050 and 0055 do not contain chemistry Information, therefore not reviewed by OPQ

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

Chemical Name	Cyclosporine
CAS number	59865-13-3
Molecular Formula	$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight	1202.61 g/mol
Chemical Names	Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl- L -leucyl-L-valyl-*N*-methyl- L -leucyl- L -ananyl-D-ananyl-*N*-methyl- L -leucyl-*N*-methyl- L -leucyl-*N*-methyl- L -valyl] Or [*R*-[*R**, *R**-(*E*)]]-Cyclic)L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*, 4-dimethyl-L-2-amino-6-octenoyl-L-α-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl) Or Cyclo[[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2- (methylamino)-oct-6-enoyl]-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]
Structural Formula	

RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Cyclosporine, USP	1	Adequate	01/19/2022
	III		(b) (4)	4	N/A	

[1] Action codes for DMF Table:

1 – DMF Reviewed	5 – Authority to reference not granted
2 –Type 1 DMF	6 – DMF not available
3 – Reviewed previously and no revision since last review	7 – Other (explain under "Comments")
4 – Sufficient information in application	

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

B. Other Documents:

N/A

EES INFORMATION

(Updated as of 11/09/2021 by Facilities Reviewer)

–

Update on 11/09/2021] MIS profile was added to the drug product manufacturing facility (b) (4) per the Genus related IR response received as SD 58 on 11/01/2021. The response to FDA comments regarding combination product was reviewed by OPMA reviewer. Applicant made adequate revision in 356h and P.3.1 by acknowledging the added drug-device combination product activities in this site. MIS profile is deemed acceptable based on the currently acceptable final DP dosage form profile (SES). All facilities are deemed acceptable to support this ANDA at this time

Overall manufacturing inspection recommendation: approve)

(b) (4)

Chemistry Review for ANDA 205894

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is adequate for approval.

B. POST APPROVAL COMMITTMENTS:

None

II. Summary of Chemistry Assessments

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

I Drug Substance

(b) (4) It is a white to almost white (b) (4) powder with the molecular formula $C_{62}H_{111}N_{11}O_{12}$ and a molecular weight of 1202.61 g/mol. (b) (4) Soluble in acetone, in methanol, (b) (4) The specifications proposed by the applicant for cyclosporine drug substance are in line with those of the DMF and USP cyclosporine drug substance monograph. DMF (b) (4) has been reviewed and is currently adequate.

II Drug Product

The proposed drug product is an ophthalmic emulsion with a strength of 0.05% (w/v), for topical administration. The drug product is packaged in single-dose (b) (4) vials (USP tight containers), with tray containing 30 or 60 vials.

Formulation consists of cyclosporine (0.05% w/v) as active ingredient. Inactive ingredients include castor oil, Polysorbate 80, Glycerin, Carbomer copolymer type A, sodium Hydroxide and water for injection. All excipients are compendial and controlled as per their monograph.

Previously, the originally proposed formulation was assessed to be Q1 to the RLD but not Q2 equivalent to the RLD (see drug product review # 3a, document titled A205894N000CHEM_3a dated 09/29/2020). In the firm's 12/17/2020 submission (eCTD

0045), (b) (4) The revised formulation is Q1/Q2 the same as the RLD formulation. Firm also manufactured 3 new exhibit batches using the revised formulation at (b) (4) scale.

Manufacturing Process

The applicant's cyclosporine ophthalmic emulsion 0.05% drug product is manufactured by (b) (4)

(b) (4) The firm's responses to these deficiencies are assessed under Section 3.2.P.3.

(b) (4)

Expiration Date

Firm proposed a 2-year expiry period for the drug product stored under the recommended room temperature storage condition. Firm has provided 6-month accelerated stability data and 12 months long-term data of 3 exhibit batches (newly manufactured at (b) (4) scale (b) (4) . All reported results are within proposed specification.

Drug Device Combination Product Assessment:

Firm has provided adequate information pertaining to drug device combination including compliance of the facility (assessed as acceptable by the facility reviewer) and comparative drop size.

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

INDICATIONS AND USAGE
Cyclosporine ophthalmic emulsion, 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

DOSAGE AND ADMINISTRATION
Instill one drop of cyclosporine ophthalmic emulsion twice a day in each eye approximately 12 hours apart.

HOW SUPPLIED
Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count (2 x 30) carton that must be dispensed intact. (30 vials NDC 0378-8760-58; 60 vials NDC 0378-8760-91).

STORAGE
Store at 15˚ to 25˚C (59˚ to 77˚F).

EXPIRATION DATE
2 years.

C. Initial and Updated Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #4	Comments
Physical Stability (solid state)	Low (12)	(b) (4)		(b) (4)
Chemical Stability	Low (12)			Stability data adequate, 12 months stability at long-term testing conditions support the proposed shelf life of 24 months
Assay	Low (18)			Stability data adequate. 12 months stability at long-term testing conditions support the proposed shelf life of 24 months

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #4	Comments
Content Uniformity	Low (12)	(b) (4)		(b) (4)
Microbial Limits	Moderate (36)			
Dissolution/IVRT (final determination refer to BE review)	Moderate (36)			
Globule Size	High (64)			
Viscosity	Moderate (36)			
Zeta-potential	Moderate (27)			
pH	Moderate (36)			
Osmolality	Moderate (27)			

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #4	Comments
		(b) (4)		(b) (4)
Surface Tension	Moderate (36)			

Reviewer's Note:
Deficiencies/comments communicated to the firm and firm's responses to those are captured from communication submitted by the firm. The assessment of firm's response is captured in green box.

59 Pages have been withheld in full as b4 (CCI/ TS) immediately following this page

Labeling & Package CMC Related Concerns:

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No N/A
(Not an OTC or Controlled Substance)

If "No," explain.

Reviewer's Assessment: **Adequate**

It should be noted the proposed package insert for the drug product was assessed and found adequate from quality perspective in Chemistry Review #01 (A205894N000CHEM R01 V04) in panorama dated 06/16/2016. Since then, there have been updates to the proposed labeling, therefore review of most recent package insert submitted in eCTD 0056 dated 01/20/2022 is performed from quality perspective. Specifically, information provided for Description and How Supplied/Storage and Handling sections are assessed and found adequate from quality perspective.

Lifecycle Management Considerations:

N/A

Overall Reviewer's Assessment and Signature: Asif Rasheed, 05/24/2021, 06/21/2021, 07/19/2021, 07/26/2021, 11/09/2021, 01/31/2022

CMC adequate.

Secondary Review Comments and Concurrence: Hongmei Li, 6/22/2021, 7/19/2021, 7/26/2021, 11/09/2021, 1/31/2022
DP CMC is adequate; Concurred.

List of Deficiencies To Be Communicated:

None

Hongmei Li

Digitally signed by Hongmei Li
Date: 2/01/2022 09:09:14AM
GUID: 54c94ca000084932f06afe87774bef34

Asif Rasheed

Digitally signed by Asif Rasheed
Date: 1/31/2022 09:30:39PM
GUID: 54943563003295d5fb908e815949f79d

[1]**Recommendation: Inadequate - CR Major**

☐ **Approval**
☐ **Information Request _____days for applicant to respond if issued by _____), OR**
☐ **Complete Response – Minor**
☒ **Complete Response – Major**

- **Major deficiency overview:** Choose an item.
  - **Justification:** The Drug Product Quality deficiencies have been classified as MAJOR because the deficiency requires justification or a change in composition of the proposed drug product. As described in Appendix B of the Guidance for Industry, *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018), a composition change or reformulation which would require manufacture of additional drug product batches with additional data, such as drug product release and stability data is considered as a major deficiency. Review of the submitted information will require substantial expenditure of FDA resources

Elemental Impurities: Comply with the USP <232/233> requirements or ICH Q3D recommendations:
☒ Yes
☐ No

Compliance with USP monographs:

- Drug Substance(s): ☒Yes; ☐No; ☐NA
- Drug Product: ☐Yes; ☐Yes*, with Differ Statement; ☐No; ☒NA

***If checked, please include the Differ Statement(s) here:**

Any approved comparability protocol: ☐Yes, How Many ____ ☒No

ANDA 205894
Review #3

[1] In FDA's January 2, 2018 response to the citizen petition submitted in Docket No. FDA-2017-P-4745, FDA stated that the petitioner's requests that implicate the nature of the data and information necessary to support approval of an ANDA for cyclosporine ophthalmic emulsion will be considered in the context of our review of the specific ANDAs. The current review has identified deficiencies in the application resulting in a complete response letter. Complete Response Letters do not constitute final agency action, as they are not the end of the decision-making process for the agency. As such, the complete response is not intended to be a final decision on any such issues.

Cyclosporine Ophthalmic Emulsion, 0.05%

Mylan Pharmaceuticals Inc.

Yang Yang, Ph.D.|Asif Rasheed, Ph.D.
Division of Product Quality and Research|Division of Liquid Based Products I
CDER/OPQ/OTR|CDER/OPQ/OLDP/DLBP

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: **205894**

2. REVIEW #: **3**

3. REVIEW DATE:

07/14/2020

4. REVIEWER: **Yang Yang, Ph.D.**
Asif Rasheed, Ph.D.

5. LAST SUBMISSION REVIEWED:

Last Submission(s) Reviewed	Document Date
Form 3674; User Fee/Coversheet; New/ANDA	11/01/2013
Patent & Exclusivity/Patent Information	01/15/2014, 07/22/2015, 07/28/2015
Patent & Exclusivity/Patent Certification	01/16/2014, 07/20/2015
Patent & Exclusivity/Patent Information; Patent & Exclusivity/Patent Certification	01/23/2014, 02/06/2014, 02/18/2014, 02/28/2014, 04/03/2014
Correspondence	07/22/2014
General Correspondence	12/22/2014, 03/18/2015
Labeling/Patient Package Insert Final; Labeling/Package Insert Draft; Quality/Response To Information Request	07/10/2015
Administrative Information	03/18/2016
Quality Response to IR (Firm submitted pictures of proposed CCS)	03/22/2016
Quality Information	07/21/2016
Quality Information	09/26/2016
Quality/Microbiology Information; Quality/Quality Information – Resubmission/After Action - Complete	02/08/2017
Quality/Response To Information Request	12/20/2017
Product Correspondence (adding 400L scale)	05/11/2018

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission Major Complete Response Amendment	06/29/2018
Multiple Category/Subcategory (SD 42)-Request for reconsideration of Major deficiency	9/27/2018
Multiple Category/Subcategory (SD 43)	10/30/2018
SD 45 Response to Bio IR on Q1/Q2	07/10/2019

SD 40 (7/12/2018): sample request
SD 41 (9/13/2018): Patent
SD 44 (11/26/2018): Patent
SD 46 (09/27/2019): Meeting request
SD 47 (12/18/2019): Product correspondence

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan PHARMACEUTICALS USA INC
Address:	781 Chestnut Ridge Road Morgantown, WV 26505
Representative:	Joseph J. Sobecki, Vice President, Regulatory Affairs
Telephone:	304-599-2595 (b) (6)
Fax	304-285-6407
Email	Joseph.Sobecki@mylan.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05%

Non-Proprietary Name (USAN): Cyclosporine Ophthalmic Emulsion 0.05%

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product	RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05% (NDA #21023 / 50790, approval date: 12/23/2002)			
Innovator Company	ALLERGAN			
Patent Data	As of 05/20/2017, there are 6 unexpired patents for this product in the *Orange Book* database.			
	Patent No	Expiry Date	Certification	**Date of Submission**
	8629111	08/27/2024	IV	01/14/2014
	8633162	08/27/2024	IV	01/23/2014
	8642556	08/27/2024	N/A	N/A
	8648048	08/27/2024	IV	02/18/2014

	8685930	08/27/2024	IV	04/03/2014
	9248191	08/27/2024	NA	NA
Exclusivity Data	Firm has certified that there are no unexpired exclusivities for RLD			

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: 0.05% w/v (0.5 mg/mL)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:

☒ Rx ☐ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed

☒ Not a NANO product

15c. PRECEDENT:

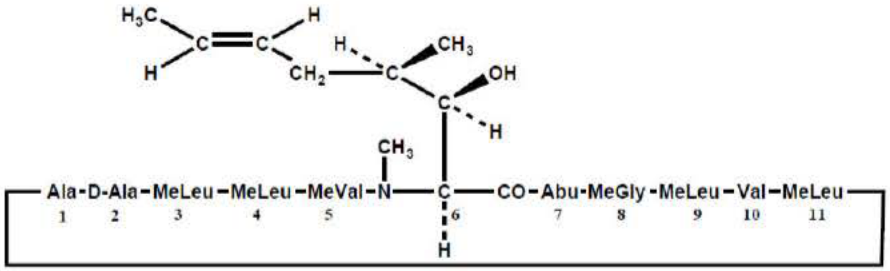
☐ The review of this ANDA establishes a precedent – TL concurrence

☒ Not a Precedent

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

Chemical Name	Cyclosporine
CAS number	59865-13-3
Molecular Formula	$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight	1202.61 g/mol

Chemistry Review Data Sheet

Chemical Names	Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl- L -leucyl-L-valyl-*N*-methyl- L -leucyl- L -ananyl-D-ananyl-*N*-methyl- L -leucyl-*N*-methyl- L -leucyl-*N*-methyl- L -valyl] Or [*R*-[*R**, *R**-(*E*)]]-Cyclic)L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*, 4-dimethyl-L-2-amino-6-octenoyl-L-α-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl) Or Cyclo[[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2- (methylamino)-oct-6-enoyl]-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Cyclosporine, USP	1	Adequate	11/08/2019
	III		(b) (4)	4	N/A	

[1] Action codes for DMF Table:

1 – DMF Reviewed	5 – Authority to reference not granted
2 –Type 1 DMF	6 – DMF not available
3 – Reviewed previously and no revision since last review	7 – Other (explain under "Comments")
4 – Sufficient information in application	

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05%	NDA 21023 / 50790	Reference Listed Drug (RLD)

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	11/02/2017	Tan, Wendy
Methods Validation	N/A		
Labeling	Adequate	8/17/2017	Lindie, Rita
Bioequivalence	Inadequate - Major	09/25/2020	Krishna Chimalakonda
Toxicology/Clinical	N/A		
EA	Categorical Exclusion Requested per 21CFR25.31	08/13/2015	Yang, Yang
Radiopharmaceutical	N/A		
Samples Requested	No		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Facility Name	Facility Address	Facility FEI	Facility Profile/ Function	OPF Recommendation Task Status
(b) (4)				Approve
				Approve
				Approve
				Approve

Chemistry Review Data Sheet

(b) (4)	
	Approve
	Approve

Chemistry Review for ANDA 205894

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Not Approvable

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

N/A

II. Summary of Chemistry Assessments

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

I Drug Substance

(b) (4) It is a white to almost white (b) (4) powder with the molecular formula $C_{62}H_{111}N_{11}O_{12}$ and a molecular weight of 1202.61 g/mole. (b) (4) Soluble in acetone, in methanol, (b) (4) The proposed specifications of cyclosporine are in line with those of DMF and USP monograph. DMF (b) (4) has been reviewed and is currently adequate. Cyclosporine is an USP article.

II Drug Product

The proposed drug product is an ophthalmic emulsion with a strength of 0.05% (w/v), intended for topical administration. The drug product is packaged in single-dose (b) (4) vials (USP tight containers), with tray containing 30 or 60 vials.

Formulation consists of cyclosporine (0.05% w/v) as API. Excipients include castor oil as solvent for API, Polysorbate 80 as non-ionic surfactant, Glycerin as tonicity agent, Carbomer as polymeric stabilizer, sodium Hydroxide for pH adjustment, and water for injection. All excipients are compendial and controlled as per their monograph. They are controlled as per the specifications provided by the DMF holders.

It should be noted that the drug product was previously assessed to be Q1/Q2 equivalent to the RLD (see drug product reviews in panorama dated 06/09/2017, 04/16/2018 and 05/11/2018).

(b) (4)

Therefore, this ANDA is not within (b) (4) range with respect to the RLD and is not Q2 for the amount of NaOH.

.

Maximum Daily Dose (MDD): 0.06 mg/day

ICH Thresholds	Reporting Threshold	Identification Threshold	Qualification Threshold
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.10%	1.0%	1.0%

Manufacturing Process

The cyclosporine ophthalmic emulsion 0.05% is manufactured by (b) (4)

(b) (4)

Expiration Date

The sponsor has provided 3-month accelerated stability data and 24 months long-term data of 3 exhibit batches with no apparent changes in appearance, assay, sterility, pH, globule size, viscosity, osmolality, and LOD, and proposed a 2-year expiry period for the drug product stored under the recommended room temperature storage condition.

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

INDICATIONS AND USAGE

Cyclosporine ophthalmic emulsion, 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

DOSAGE AND ADMINISTRATION (MDD 0.06 mg/day)

Instill one drop of cyclosporine ophthalmic emulsion twice a day in each eye approximately 12 hours apart.

HOW SUPPLIED

Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count (2 x 30) carton that must be dispensed intact. (30 vials NDC 0378-8760-58; 60 vials NDC 0378-8760-91).

STORAGE

Store at 15˚ to 25˚C (59˚ to 77˚F).

TENTATIVE EXPIRATION DATE

2 years.

C. Initial and Updated Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments
Physical Stability (solid state)	Low (12)	(b) (4)	Low	(b) (4)
Chemical Stability	Low (12)		Low	
Assay	Low (18)		Low	
Content Uniformity	Low (12)		Low	
Microbial Limits	Moderate (36)		Low	
Dissolution/IVRT (final	Moderate (36)		Moderate	

Executive Summary Section

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments
determination refer to BE review)		(b) (4)		(b) (4)
Globule Size	High (64)		Medium	
Viscosity	Moderate (36)		Medium	
Zeta-potential	Moderate (27)		Low	
pH	Moderate (36)		Low	
Osmolality	Moderate (27)		Low	
Surface Tension	Moderate (36)		Low	

Executive Summary Section

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments
		(b) (4)		(b) (4)

D. Basis for Approvability or Not-Approval Recommendation

CMC Not approvable
BE is Pending.
Labeling is adequate.
Microbiology is adequate.

Note: In this review document, color-coded background approach has been used to distinguish the information provided by the sponsor and reviewers' assessment. Following are the background colors selected for distinctions: grey background for executive summary that includes critical elements of the review; white background for information provided by the sponsor; green background for reviewer assessments. Font color for the deficiency has been chosen red. Most of the tables have been taken from the sponsor submission and modified as needed to assist in the application evaluation.

30 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Labeling & Package CMC Related Concerns:

***Reviewer's Assessment*: Adequate**

Lifecycle Management Considerations:

N/A

Overall Reviewer's Assessment and Signature: Yang Yang, Ph.D., 11/14/2018, Asif Rasheed, 01/29/2020

CMC inadequate.

Secondary Review Comments and Concurrence: Jin Xu, 01/28/2019, Shin Grace Chou, 02/04/2020

I concur.

(b) (4)

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Asif Rasheed

Digitally signed by Asif Rasheed
Date: 9/29/2020 04:34:09PM
GUID: 54943563003295d5fb908e815949f79d

Shin Chou

Digitally signed by Shin Chou
Date: 9/29/2020 07:07:58PM
GUID: 51defe4b00010821ff38f29e384b0ab5

CHEMISTRY REVIEW

A. Check List *(once you check a "Yes" from top down, skip the rest afterward):*

- First Generic? Yes: ☐ No: ☒
- MR Product? Yes: ☒ No: ☐
- Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD? Yes: ☐ No: ☒
- Major Formulation/ Mfg. Process Change Yes: ☐ No: ☒

B. Review Tier *(3 Tier if a "Yes" and 2 Tier if all "No" are checked in A)*: **3 Tier:** ☒ **2 Tier:** ☐

C. Approvability: – ***Not Approvable, CR-major.***

ANDA 205894

Cyclosporine Ophthalmic Emulsion, 0.05%

Mylan Pharmaceuticals Inc.

Yang Yang, Ph.D.
Division of Product Quality and Research
CDER/OPQ/OTR

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: **205894**

2. REVIEW #: **2a**

3. REVIEW DATE: **08/20/2015; 10/21/2016; 05/20/2017; 09/29/2017**

4. REVIEWER: **Yang Yang, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Form 3674; User Fee/Coversheet; New/ANDA	11/01/2013
Patent & Exclusivity/Patent Information	01/15/2014, 07/22/2015, 07/28/2015
Patent & Exclusivity/Patent Certification	01/16/2014, 07/20/2015
Patent & Exclusivity/Patent Information; Patent & Exclusivity/Patent Certification	01/23/2014, 02/06/2014, 02/18/2014, 02/28/2014, 04/03/2014
Correspondence	07/22/2014
General Correspondence	12/22/2014, 03/18/2015
Labeling/Patient Package Insert Final; Labeling/Package Insert Draft; Quality/Response To Information Request	07/10/2015
Quality/Microbiology Information; Quality/Quality Information – Resubmission/After Action - Complete	02/08/2017
Quality/Response To Information Request	12/20/2017

7. NAME & ADDRESS OF APPLICANT[1]:

[1] SOURCE: Most recent FDA Form 356h, submission date 11/01/2013

Chemistry Review Data Sheet

Name:	Mylan PHARMACEUTICALS USA INC
Address:	781 Chestnut Ridge Road Morgantown, WV 26505
Representative:	Joseph J. Sobecki, Vice President, Regulatory Affairs
Telephone:	304-599-2595 (b) (6)
Fax	304-285-6407
Email	Joseph.Sobecki@mylan.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05%

Non-Proprietary Name (USAN): Cyclosporine Ophthalmic Emulsion 0.05%

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product	RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05% (NDA #21023 / 50790, approval date: 12/23/2002)			
Innovator Company	ALLERGAN			
Patent Data	As of 05/20/2017, there are 6 unexpired patents for this product in the *Orange Book* database.			
	Patent No	**Expiry Date**	**Certification**	**Date of Submission**
	8629111	08/27/2024	IV	01/14/2014
	8633162	08/27/2024	IV	01/23/2014
	8642556	08/27/2024	N/A	N/A
	8648048	08/27/2024	IV	02/18/2014
	8685930	08/27/2024	IV	04/03/2014
	9248191	08/27/2024	NA	NA
Exclusivity Data	Firm has certified that there are no unexpired exclusivities for RLD			

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: 0.05% w/v (0.5 mg/mL)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:

☒ Rx ☐ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed

☒ Not a NANO product

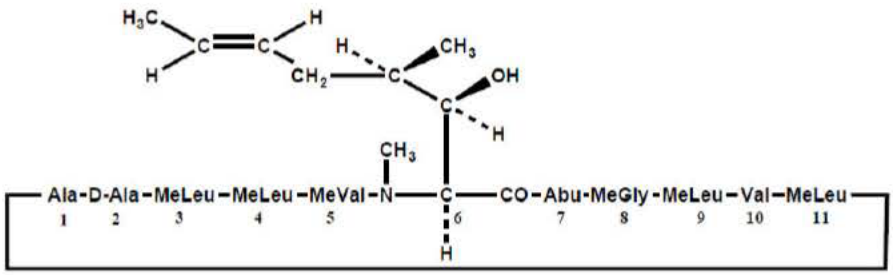
15c. PRECEDENT:

☐ The review of this ANDA establishes a precedent – TL concurrence

☒ Not a Precedent

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

Chemical Name	Cyclosporine
CAS number	59865-13-3
Molecular Formula	$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight	1202.61 g/mol
Chemical Names	Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl- L -leucyl-L-valyl-*N*-methyl- L -leucyl- L -ananyl-D-ananyl-*N*-methyl- L -leucyl-*N*-methyl- L -leucyl-*N*-methyl- L -valyl] Or [*R*-[*R**, *R**-(*E*)]]-Cyclic)L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*, 4-dimethyl-L-2-amino-6-octenoyl-L-α-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl) Or Cyclo[[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2- (methylamino)-oct-6-enoyl]-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]

Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s)[2]:

DMF #	Type	HOLDER	ITEM REFERENCED	Code	STATUS[1]	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Cyclosporine, USP	1	adequate	As of 04/14/2017 by Bhattacharyya, Siba P
	III		(b) (4)	4	N/A	

[1] Action codes for DMF Table:

1 – DMF Reviewed	5 – Authority to reference not granted
2 –Type 1 DMF	6 – DMF not available
3 – Reviewed previously and no revision since last review	7 – Other (explain under "Comments")
4 – Sufficient information in application	

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05%	NDA 21023 / 50790	Reference Listed Drug (RLD)

[2] SOURCE: Most recent FDA Form 356h, submission date 11/01/2013

18. STATUS

CONSULTS/ CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		Adequate	5/30/2017	Tan, Wendy
Methods Validation		N/A		
Labeling		Adequate	8/17/2017	Lindie, Rita
Bioequivalence	Dissolution	Inadequate		
	Bioequivalence	Inadequate		
Toxicology/Clinical		N/A		
EA		Categorical Exclusion Requested per 21CFR25.31	08/13/2015	Yang, Yang
Radiopharmaceutical		N/A		
Samples Requested		No		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Facility Name	Facility Address	Facility FEI	Facility Profile/ Function	OPF Recommendation Task Status
(b) (4)				Complete
				Complete
				New
				Complete
				New
				Complete
				Complete

Chemistry Review for ANDA 205894

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Not Approvable with CR letter

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

N/A

II. Summary of Chemistry Assessments

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

I Drug Substance

(b) (4) It is a white (b) (4) powder with the molecular formula $C_{62}H_{111}N_{11}O_{12}$ and a molecular weight of 1202.61 g/mole. (b) (4) Soluble in acetone, in methanol, (b) (4) The proposed specifications of cyclosporine are in line with those of DMF and USP monograph. However, this DMF (b) (4) has not been reviewed. Cyclosporine is an USP article.

II Drug Product (Not to be released under FOIA)

The proposed drug product is an ophthalmic emulsion with strengths of 0.05% (w/v), intended for topical administration. The drug product is packaged in single-dose (b) (4) vials (USP tight containers), with tray containing 30 or 60 vials.

Formulation consists of cyclosporine (0.05% w/v) as API. Excipients include caster oil as solvent for API, Polysorbate 80 as non-ionic surfactant, Glycerin as tonicity agent, Carbomer as polymeric stabilizer, sodium Hydroxide for pH adjustment, and water. All excipients are compendial and controlled as per their monograph. They are controlled as per the specifications provided by the DMF holders.

The proposed product is the same in design and composition to RLD based on information available to the agency (Q1/Q2/Q3 equivalent). Therefore, drug release rate and mechanism

of performance is expected to be comparable to RLD.

Maximum Daily Dose (MDD): 0.06 mg/day

ICH Thresholds	Reporting Threshold	Identification Threshold	Qualification Threshold
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.10%	1.0%	1.0%

Manufacturing Process

The cyclosporine ophthalmic emulsion 0.05% is manufactured (b) (4)

(b) (4)

(b) (4)

[redacted]

Expiration Date

The sponsor has provided 3-month accelerated stability data and 18-24 months long-term data of 3 batches with no apparent changes in appearance, assay, sterility, pH, globule size, viscosity, osmolality, and LOD, and proposed a 2-year expiry period for the drug product stored under the recommended room temperature storage condition. However, neither drug degradation nor deliverable volume was reported under any storage conditions.

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

INDICATIONS AND USAGE

Cyclosporine ophthalmic emulsion, 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

DOSAGE AND ADMINISTRATION (MDD 0.06 mg/day)

Instill one drop of cyclosporine ophthalmic emulsion twice a day in each eye approximately 12 hours apart.

HOW SUPPLIED

Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count (2 x 30) carton that must be dispensed intact. (30 vials NDC 0378-8760-58; 60 vials NDC 0378-8760-91)

STORAGE

Store at 15˚ to 25˚C (59˚ to 77˚F).

TENTATIVE EXPIRATION DATE

2 years based on 3-month accelerated stability data.

C. Initial and Updated Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments
		(b) (4)		(b) (4)
Physical Stability (solid state)	Low (12)		Low	
Chemical Stability	Low (12)		Low	
Assay	Low (18)		Low	
Content Uniformity	Low (12)		Low	
Microbial Limits	Moderate (36)		Low	
Dissolution/IVRT (final determination refer to BE review)	Moderate (36)		Moderate	
Globule Size	High (64)		Low	
Viscosity	Moderate (36)		Low	
Zeta-potential	Moderate (27)		Low	
pH	Moderate (36)		Low	

Executive Summary Section

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments
		(b) (4)		(b) (4)
Osmolality	Moderate (27)		Low	
Surface Tension	Moderate (36)		Low	

D. Basis for Approvability or Not-Approval Recommendation

CMC Not approvable, with CR Letter
BE Inadequate.
Labeling is adequate.
Microbiology is adequate.

Note: In this review document, color-coded background approach has been used to distinguish the information provided by the sponsor and reviewers' assessment. Following are the background colors selected for distinctions: grey background for executive summary that includes critical elements of the review; white background for information provided by the sponsor; green background for reviewer assessments. Font color for the deficiency has been chosen red. Most of the tables have been taken from the sponsor submission and modified as needed to assist in the application evaluation.

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	Restasis® (Cyclosporine) Ophthalmic Emulsion 0.05%
Non-Proprietary Name of Drug Product	Cyclosporine Ophthalmic Emulsion 0.05%
Non-Proprietary Name of Drug Substance	Cyclosporine USP
Company Name	Mylan Pharmaceuticals Inc.
Dosage Form	Emulsion
Strength(s)	0.05%
Route of Administration	Ophthalmic
Proposed Indication(s)	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.
Maximum Daily Dose	0.06 mg/day

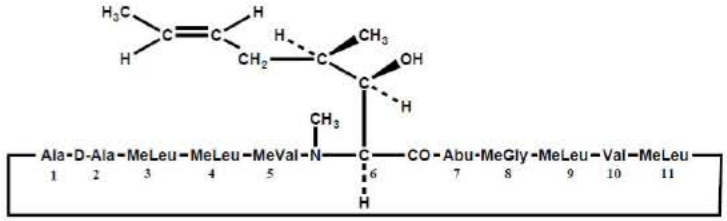
2.3.S DRUG SUBSTANCE [Cyclosporine USP]

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Firm's Response:

USAN: Cyclosporine
CAS number: 59865-13-3
Chemical Family: Immunomodulator
Molecular Formula: $C_{62}H_{111}N_{11}O_{12}$
Molecular Weight: 1202.61g/mole
Structural Formula:



79 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

A **APPENDICES**

A.1 ***Facilities and Equipment (biotech only): N/A***

A.2 ***Adventitious Agents Safety Evaluation: N/A***

A.3 ***Novel Excipients: N/A***

A.4 ***Nanotechnology Product Information: N/A***

A.5 ***Precedent Setting Information: N/A***

R **REGIONAL INFORMATION**

R.1 ***Executed Batch Records (Refer to Sections S.4 and P.5)***

R.2 ***Comparability Protocols***

Reviewer's Assessment (Review #1):

No comparability protocol is proposed.

R.3 ***Methods Validation Package (Refer to Sections S.4 and P.5)***

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)
Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No ☒ N/A If "No," explain.

e) For solid oral drug products, only: drug product length(s) of commercial batch(es): **N/A**

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: **N/A**

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification Provided: ☒ Yes ☐ No

Exclusivity Provided: ☒ Yes ☐ No

Debarment Certification Provided: ☒ Yes ☐ No

cGMP Statement Provided: ☒ Yes ☐ No

Reprocessing Statement Provided: ☒ Yes ☐ No

Letters of Authorization Provided: ☒ Yes ☐ No

Request for Bio-waiver Provided: ☒ Yes ☐ No

Citizen Petition and/or Control Request Linked to the Application: N/A

Environmental Impact Considerations/Categorical Exclusions Provided: ☒ Yes ☐ No

2 Pages have been withheld in full as b4 (CCI/ TS) immediately following this page

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

HFD-940/Yang, Yang, Ph.D. / Reviewer 08/20/2015; 12/18/2015; 06/14/2016; 10/21/2016; 05/20/2017; 09/27/2017
HFD-940/Ashraf, Muhammad, Ph.D. /Secondary Reviewer/10/21/2016; 6/2/2017
HFD-940/Cai, Bing, Ph.D./Tertiary Reviewer/
HFD-617/Robert Hallenberg/ PM/

TYPE OF LETTER: Not approvable CR-major.

Yang Yang

Digitally signed by Yang Yang
Date: 5/10/2018 09:21:17AM
GUID: 542e18bd0004452b6a70350e55371bcd

Muhammad Ashraf

Digitally signed by Muhammad Ashraf
Date: 5/11/2018 12:32:52PM
GUID: 508da705000289defcccfe6abe65951b

CHEMISTRY REVIEW

A. Check List *(once you check a "Yes" from top down, skip the rest afterward):*

- First Generic? Yes: ☐ No: ☒
- MR Product? Yes: ☒ No: ☐
- Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD? Yes: ☐ No: ☒
- Major Formulation/ Mfg. Process Change Yes: ☐ No: ☒

B. Review Tier *(3 Tier if a "Yes" and 2 Tier if all "No" are checked in A)*: **3 Tier:** ☒ **2 Tier:** ☐

C. Approvability: – ***Not Approvable, CR-major.***

ANDA 205894

Cyclosporine Ophthalmic Emulsion, 0.05%

Mylan Pharmaceuticals Inc.

Yang Yang, Ph.D.
Division of Product Quality and Research
CDER/OPQ/OTR

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: **205894**

2. REVIEW #: **2a**

3. REVIEW DATE: **08/20/2015; 10/21/2016; 05/20/2017; 09/29/2017**

4. REVIEWER: **Yang Yang, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Form 3674; User Fee/Coversheet; New/ANDA	11/01/2013
Patent & Exclusivity/Patent Information	01/15/2014, 07/22/2015, 07/28/2015
Patent & Exclusivity/Patent Certification	01/16/2014, 07/20/2015
Patent & Exclusivity/Patent Information; Patent & Exclusivity/Patent Certification	01/23/2014, 02/06/2014, 02/18/2014, 02/28/2014, 04/03/2014
Correspondence	07/22/2014
General Correspondence	12/22/2014, 03/18/2015
Labeling/Patient Package Insert Final; Labeling/Package Insert Draft; Quality/Response To Information Request	07/10/2015

7. NAME & ADDRESS OF APPLICANT[1]:

Name:	Mylan PHARMACEUTICALS USA INC
Address:	781 Chestnut Ridge Road Morgantown, WV 26505

[1] SOURCE: Most recent FDA Form 356h, submission date 11/01/2013

Chemistry Review Data Sheet

Representative:	Joseph J. Sobecki, Vice President, Regulatory Affairs
Telephone:	304-599-2595 (b) (6)
Fax	304-285-6407
Email	Joseph.Sobecki@mylan.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05%

Non-Proprietary Name (USAN): Cyclosporine Ophthalmic Emulsion 0.05%

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product	RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05% (NDA #21023 / 50790, approval date: 12/23/2002)			
Innovator Company	ALLERGAN			
Patent Data	As of 05/20/2017, there are 6 unexpired patents for this product in the *Orange Book* database.			
	Patent No	**Expiry Date**	**Certification**	**Date of Submission**
	8629111	08/27/2024	IV	01/14/2014
	8633162	08/27/2024	IV	01/23/2014
	8642556	08/27/2024	N/A	N/A
	8648048	08/27/2024	IV	02/18/2014
	8685930	08/27/2024	IV	04/03/2014
	9248191	08/27/2024	NA	NA
Exclusivity Data	Firm has certified that there are no unexpired exclusivities for RLD			

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: 0.05% w/v (0.5 mg/mL)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:

☒ Rx ☐ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed

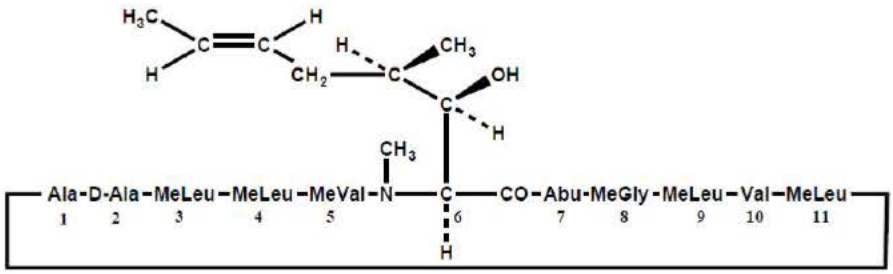
☒ Not a NANO product

15c. PRECEDENT:

☐ The review of this ANDA establishes a precedent – TL concurrence

☒ Not a Precedent

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

Chemical Name	Cyclosporine
CAS number	59865-13-3
Molecular Formula	$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight	1202.61 g/mol
Chemical Names	Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl- L -leucyl-L-valyl-*N*-methyl- L -leucyl- L -ananyl-D-ananyl-*N*-methyl- L -leucyl-*N*-methyl- L -leucyl-*N*-methyl- L -valyl] Or [*R*-[*R**, *R**-(*E*)]]-Cyclic)L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*, 4-dimethyl-L-2-amino-6-octenoyl-L-α-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl) Or Cyclo[[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2- (methylamino)-oct-6-enoyl]-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s)[2]:

DMF #	Type	HOLDER	ITEM REFERENCED	Code	STATUS[1]	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Cyclosporine, USP	1	adequate	As of 04/14/2017 by Bhattacharyya, Siba P
	III		(b) (4)	4	N/A	

[1] Action codes for DMF Table:

1 – DMF Reviewed	5 – Authority to reference not granted
2 –Type 1 DMF	6 – DMF not available
3 – Reviewed previously and no revision since last review	7 – Other (explain under "Comments")
4 – Sufficient information in application	

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05%	NDA 21023 / 50790	Reference Listed Drug (RLD)

[2] SOURCE: Most recent FDA Form 356h, submission date 11/01/2013

18. STATUS

CONSULTS/ CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		Adequate	5/30/2017	Tan, Wendy
Methods Validation		N/A		
Labeling		Adequate	8/17/2017	Lindie, Rita
Bioequivalence	Dissolution	Inadequate		
	Bioequivalence	Inadequate		
Toxicology/Clinical		N/A		
EA		Categorical Exclusion Requested per 21CFR25.31	08/13/2015	Yang, Yang
Radiopharmaceutical		N/A		
Samples Requested		No		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Facility Name	Facility Address	Facility FEI	Facility Profile/ Function	OPF Recommendation Task Status
(b) (4)				Complete
				Complete
				New
				Complete
				New
				Complete
				Complete

Chemistry Review for ANDA 205894

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Not Approvable with CR letter

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

N/A

II. Summary of Chemistry Assessments

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

I Drug Substance

(b) (4) It is a white (b) (4) powder with the molecular formula $C_{62}H_{111}N_{11}O_{12}$ and a molecular weight of 1202.61 g/mole. (b) (4) Soluble in acetone, in methanol (b) (4) . The proposed specifications of cyclosporine are in line with those of DMF and USP monograph. However, this DMF (b) (4) has not been reviewed. Cyclosporine is an USP article.

II Drug Product (Not to be released under FOIA)

The proposed drug product is an ophthalmic emulsion with strengths of 0.05% (w/v), intended for topical administration. The drug product is packaged in single-dose (b) (4) vials (USP tight containers), with tray containing 30 or 60 vials.

Formulation consists of cyclosporine (0.05% w/v) as API. Excipients include caster oil (b) (4) Polysorbate 80 (b) (4) Glycerin (b) (4) Carbomer (b) (4) sodium Hydroxide for pH adjustment, and water. All excipients are compendial and controlled as per their monograph. They are controlled as per the specifications provided by the DMF holders.

The proposed product is the same in design and composition to RLD based on information available to the agency (Q1/Q2/Q3 equivalent). Therefore, drug release rate and mechanism

of performance is expected to be comparable to RLD.

Maximum Daily Dose (MDD): 0.06 mg/day

ICH Thresholds	Reporting Threshold	Identification Threshold	Qualification Threshold
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.10%	1.0%	1.0%

Manufacturing Process

The cyclosporine ophthalmic emulsion 0.05% is manufactured (b) (4)

(b) (4)

(b) (4)

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

INDICATIONS AND USAGE

Cyclosporine ophthalmic emulsion, 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

DOSAGE AND ADMINISTRATION (MDD 0.06 mg/day)

Instill one drop of cyclosporine ophthalmic emulsion twice a day in each eye approximately 12 hours apart.

HOW SUPPLIED

Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count (2 x 30) carton that must be dispensed intact. (30 vials NDC 0378-8760-58; 60 vials NDC 0378-8760-91)

STORAGE

Store at 15˚ to 25˚C (59˚ to 77˚F).

TENTATIVE EXPIRATION DATE

2 years based on 3-month accelerated stability data.

C. Initial and Updated Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments (b) (4)	Updated Risk Ranking after Review Cycle #1	Comments (b) (4)
Physical Stability (solid state)	Low (12)		Low	
Chemical Stability	Low (12)		Low	
Assay	Low (18)		Low	
Content Uniformity	Low (12)		Low	
Microbial Limits	Moderate (36)		Low	
Dissolution/IVRT (final determination refer to BE review)	Moderate (36)		Moderate	
Globule Size	High (64)		Low	
Viscosity	Moderate (36)		Low	
Zeta-potential	Moderate (27)		Low	
pH	Moderate (36)		Low	

Executive Summary Section

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments
		(b) (4)		(b) (4)
Osmolality	Moderate (27)		Low	
Surface Tension	Moderate (36)		Low	

D. Basis for Approvability or Not-Approval Recommendation

CMC Not approvable, with CR Letter
BE Inadequate.
Labeling is adequate.
Microbiology is adequate.

Note: In this review document, color-coded background approach has been used to distinguish the information provided by the sponsor and reviewers' assessment. Following are the background colors selected for distinctions: grey background for executive summary that includes critical elements of the review; white background for information provided by the sponsor; green background for reviewer assessments. Font color for the deficiency has been chosen red. Most of the tables have been taken from the sponsor submission and modified as needed to assist in the application evaluation.

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	Restasis® (Cyclosporine) Ophthalmic Emulsion 0.05%
Non-Proprietary Name of Drug Product	Cyclosporine Ophthalmic Emulsion 0.05%
Non-Proprietary Name of Drug Substance	Cyclosporine USP
Company Name	Mylan Pharmaceuticals Inc.
Dosage Form	Emulsion
Strength(s)	0.05%
Route of Administration	Ophthalmic
Proposed Indication(s)	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.
Maximum Daily Dose	0.06 mg/day

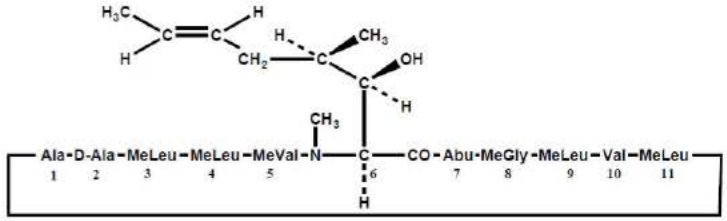
2.3.S DRUG SUBSTANCE [Cyclosporine USP]

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Firm's Response:

USAN: Cyclosporine
CAS number: 59865-13-3
Chemical Family: Immunomodulator
Molecular Formula: $C_{62}H_{111}N_{11}O_{12}$
Molecular Weight: 1202.61g/mole
Structural Formula:



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2.3.P DRUG PRODUCT [Cyclosporine Ophthalmic Emulsion, 0.05%]

2.3.P.1 Description and Composition of the Drug Product

What are the components and composition of the final product? What is the function(s) of each excipient? Does any excipient exceed the IIG limit for this route of administration?

Firm's Response:

Component	0.05%			Pharmaceutical Function	IIG Limit[1]
	Quantity (mg/mL)	% w/v	% w/w[2]		
Active Ingredient					
Cyclosporine, USP	0.500	(b) (4)		Active	-
Inactive Ingredients					
Castor Oil, NF	(b) (4)	(b) (4)		(b) (4)	5%
Polysorbate 80, NF					(b) (4)
Glycerin USP	(b) (4)				2.2%
(Carbomer Co-polymer Type A)[3]	(b) (4)				(b) (4) (b) (4)
(b) (4) Sodium Hydroxide, NF[4]				pH adjusting agent	
Water for Injection, USP				(b) (4)	-
					(b) (4)

All of the excipients used in Mylan's Cyclosporine ophthalmic emulsion, 0.05% are within the limits for an ophthalmic route of administration as listed in the Inactive Ingredient Database. A comparison is summarized in the table below. The inactive ingredients do not affect the safety of the proposed drug product and the requirements outlined in 21 CFR 314.94(a)(9)(iv) have been satisfied.

Reviewer's Comment (Review #1):

The proposed product has the same formulation design and contains same amount of each component as the RLD (Restasis®). (b) (4)

64 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

A **APPENDICES**

A.1 ***Facilities and Equipment (biotech only): N/A***

A.2 ***Adventitious Agents Safety Evaluation: N/A***

A.3 ***Novel Excipients: N/A***

A.4 ***Nanotechnology Product Information: N/A***

A.5 ***Precedent Setting Information: N/A***

R **REGIONAL INFORMATION**

R.1 ***Executed Batch Records (Refer to Sections S.4 and P.5)***

R.2 ***Comparability Protocols***

Reviewer's Assessment (Review #1):

No comparability protocol is proposed.

R.3 ***Methods Validation Package (Refer to Sections S.4 and P.5)***

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)
Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No ☒ N/A If "No," explain.

e) For solid oral drug products, only: drug product length(s) of commercial batch(es): **N/A**

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: **N/A**

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification Provided: ☒ Yes ☐ No

Exclusivity Provided: ☒ Yes ☐ No

Debarment Certification Provided: ☒ Yes ☐ No

cGMP Statement Provided: ☒ Yes ☐ No

Reprocessing Statement Provided: ☒ Yes ☐ No

Letters of Authorization Provided: ☒ Yes ☐ No

Request for Bio-waiver Provided: ☒ Yes ☐ No

Citizen Petition and/or Control Request Linked to the Application: N/A

Environmental Impact Considerations/Categorical Exclusions Provided: ☒ Yes ☐ No

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

HFD-940/Yang, Yang, Ph.D. / Reviewer 08/20/2015; 12/18/2015; 06/14/2016; 10/21/2016; 05/20/2017; 09/27/2017
HFD-940/Ashraf, Muhammad, Ph.D. /Secondary Reviewer/10/21/2016; 6/2/2017
HFD-940/Cai, Bing, Ph.D./Tertiary Reviewer/
HFD-617/Robert Hallenberg/ PM/

TYPE OF LETTER: Not approvable CR-major.

Yang Yang

Digitally signed by Yang Yang
Date: 4/13/2018 10:35:18AM
GUID: 542e18bd0004452b6a70350e55371bcd

Muhammad Ashraf

Digitally signed by Muhammad Ashraf
Date: 4/16/2018 01:15:40PM
GUID: 508da705000289defcccfe6abe65951b
Comments: Approved

CHEMISTRY REVIEW

A. Check List *(once you check a "Yes" from top down, skip the rest afterward):*

- First Generic? Yes: ☐ No: ☒
- MR Product? Yes: ☒ No: ☐
- Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD? Yes: ☐ No: ☒
- Major Formulation/ Mfg. Process Change Yes: ☐ No: ☒

B. Review Tier *(3 Tier if a "Yes" and 2 Tier if all "No" are checked in A)*: **3 Tier:** ☒ **2 Tier:** ☐

C. Approvability: – ***Not Approvable, Information Request 30 Days***

ANDA 205894

Cyclosporine Ophthalmic Emulsion, 0.05%

Mylan Pharmaceuticals Inc.

Yang Yang, Ph.D.
Division of Product Quality and Research
CDER/OPQ/OTR

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: **205894**

2. REVIEW #: **1b**

3. REVIEW DATE: **August 20, 2015; October 21, 2016**

4. REVIEWER: **Yang Yang, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Form 3674; User Fee/Coversheet; New/ANDA	11/01/2013
Patent & Exclusivity/Patent Information	01/15/2014, 07/22/2015, 07/28/2015
Patent & Exclusivity/Patent Certification	01/16/2014, 07/20/2015
Patent & Exclusivity/Patent Information; Patent & Exclusivity/Patent Certification	01/23/2014, 02/06/2014, 02/18/2014, 02/28/2014, 04/03/2014
Correspondence	07/22/2014
General Correspondence	12/22/2014, 03/18/2015
Labeling/Patient Package Insert Final; Labeling/Package Insert Draft; Quality/Response To Information Request	07/10/2015

7. NAME & ADDRESS OF APPLICANT[1]:

Name:	Mylan PHARMACEUTICALS USA INC
Address:	781 Chestnut Ridge Road Morgantown, WV 26505

[1] SOURCE: Most recent FDA Form 356h, submission date 11/01/2013

Chemistry Review Data Sheet

Representative:	Joseph J. Sobecki, Vice President, Regulatory Affairs
Telephone:	304-599-2595 (b) (6)
Fax	304-285-6407
Email	Joseph.Sobecki@mylan.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05%

Non-Proprietary Name (USAN): Cyclosporine Ophthalmic Emulsion 0.05%

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product	RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05% (NDA #21023 / 50790, approval date: 12/23/2002)			
Innovator Company	ALLERGAN			
Patent Data	As of 10/21/2016, there are 6 unexpired patents for this product in the *Orange Book* database.			
	Patent No	**Expiry Date**	**Certification**	**Date of Submission**
	8629111	08/27/2024	IV	01/14/2014
	8633162	08/27/2024	IV	01/23/2014
	8642556	08/27/2024	N/A	N/A
	8648048	08/27/2024	IV	02/18/2014
	8685930	08/27/2024	IV	04/03/2014
	9248191	08/27/2024	NA	NA
Exclusivity Data	Firm has certified that there are no unexpired exclusivities for RLD			

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Emulsion

12. STRENGTH/POTENCY: 0.05% w/v (0.5 mg/mL)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:

☒ Rx ☐ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed

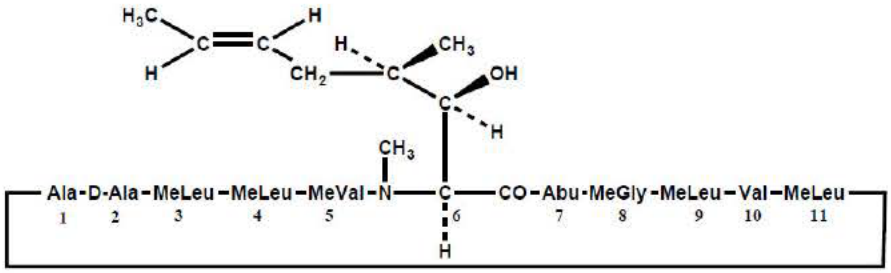
☒ Not a NANO product

15c. PRECEDENT:

☐ The review of this ANDA establishes a precedent – TL concurrence

☒ Not a Precedent

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

Chemical Name	Cyclosporine
CAS number	59865-13-3
Molecular Formula	$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight	1202.61 g/mol
Chemical Names	Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl- L -leucyl-L-valyl-*N*-methyl- L -leucyl- L -ananyl-D-ananyl-*N*-methyl- L -leucyl-*N*-methyl- L -leucyl-*N*-methyl- L -valyl] Or [*R*-[*R**, *R**-(*E*)]]-Cyclic)L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*, 4-dimethyl-L-2-amino-6-octenoyl-L-α-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl) Or Cyclo[[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2- (methylamino)-oct-6-enoyl]-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s) [2]:

DMF #	Type	HOLDER	ITEM REFERENCED	Code	STATUS[1]	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Cyclosporine, USP	7	Inadequate	8/22/16
	III		(b) (4)	4	N/A	

[1] Action codes for DMF Table:

1 – DMF Reviewed	5 – Authority to reference not granted
2 –Type 1 DMF	6 – DMF not available
3 – Reviewed previously and no revision since last review	7 – Other (explain under "Comments")
4 – Sufficient information in application	

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RESTASIS® (Cyclosporine) Ophthalmic Emulsion 0.05%	NDA 21023 / 50790	Reference Listed Drug (RLD)

[2] SOURCE: Most recent FDA Form 356h, submission date 11/01/2013

18. STATUS

CONSULTS/ CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		Inadequate	10/14/16	Wendy Tan
Methods Validation		N/A		
Labeling		Inadequate	3/4/16	Rita Lindie
Bioequivalence	Dissolution	Pending		
	Bioequivalence	Inadequate	10/18/16	Krishna Chimalakonda
Toxicology/Clinical		N/A		
EA		Categorical Exclusion Requested per 21CFR25.31	08/13/2015	Yang, Yang
Radiopharmaceutical		N/A		
Samples Requested		No		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Facility Name	Facility Address	Facility FEI	Facility Profile/ Function	OPF Recommendation Task Status
(b) (4)				Complete
				Complete
				New
				Complete
				New
				Complete
				Complete

Chemistry Review Data Sheet

(b) (4)				

Appears this way on original

Chemistry Review for ANDA 205894

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable – Information Request 30 days

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

N/A

II. Summary of Chemistry Assessments

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

I Drug Substance

(b) (4) It is a white (b) (4) powder with the molecular formula $C_{62}H_{111}N_{11}O_{12}$ and a molecular weight of 1202.61 g/mole. (b) (4) Soluble in acetone, in methanol, (b) (4) The proposed specifications of cyclosporine are in line with those of DMF and USP monograph. However, this DMF (b) (4) has not been reviewed. Cyclosporine is an USP article.

II Drug Product (Not to be released under FOIA)

The proposed drug product is an ophthalmic emulsion with strengths of 0.05% (w/v), intended for topical administration. The drug product is packaged in single-dose (b) (4) vials (USP tight containers), with tray containing 30 or 60 vials.

Formulation consists of cyclosporine (0.05% w/v) as API. Excipients include caster oil (b) (4) Polysorbate 80 (b) (4) Glycerin (b) (4) Carbomer (b) (4) sodium Hydroxide for pH adjustment, and water. All excipients are compendial and controlled as per their monograph. They are controlled as per the specifications provided by the DMF holders.

The proposed product is the same in design and composition to RLD based on information available to the agency (Q1/Q2/Q3 equivalent). Therefore, drug release rate and mechanism

of performance is expected to be comparable to RLD.

Maximum Daily Dose (MDD): 0.06 mg/day

ICH Thresholds	Reporting Threshold	Identification Threshold	Qualification Threshold
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.10%	1.0%	1.0%

Manufacturing Process

The cyclosporine ophthalmic emulsion 0.05% is manufactured (b) (4)

(b) (4)

(b) (4)

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

INDICATIONS AND USAGE
Cyclosporine ophthalmic emulsion, 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

DOSAGE AND ADMINISTRATION (MDD 0.06 mg/day)
Instill one drop of cyclosporine ophthalmic emulsion twice a day in each eye approximately 12 hours apart.

HOW SUPPLIED
Cyclosporine Ophthalmic Emulsion, 0.05% is available in sterile, preservative-free single-use blow molded vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine Ophthalmic Emulsion is also provided in a 60 count (2 x 30) carton that must be dispensed intact. (30 vials NDC 0378-8760-58; 60 vials NDC 0378-8760-91)

STORAGE

Store at 15˚ to 25˚C (59˚ to 77˚F).

TENTATIVE EXPIRATION DATE

2 years based on 3-month accelerated stability data.

Executive Summary Section

C. Initial and Updated Risk Assessment

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments
Physical Stability (solid state)	Low (12)	(b) (4)	Low	(b) (4)
Chemical Stability	Low (12)		Low	
Assay	Low (18)		Low	
Content Uniformity	Low (12)		Low	
Microbial Limits	Moderate (36)		Low	
Dissolution/IVRT (final determination refer to BE review)	Moderate (36)		Moderate	
Globule Size	High (64)		Low	
Viscosity	Moderate (36)		Moderate	
Zeta-potential	Moderate (27)		Moderate	
pH	Moderate (36)		Low	

Executive Summary Section

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments
		(b) (4)		(b) (4)
Osmolality	Moderate (27)		Low	
Surface Tension	Moderate (36)		Low	

D. Basis for Approvability or Not-Approval Recommendation

Not approvable, information request 30 days.

Note: In this review document, color-coded background approach has been used to distinguish the information provided by the sponsor and reviewers' assessment. Following are the background colors selected for distinctions: grey background for executive summary that includes critical elements of the review; white background for information provided by the sponsor; green background for reviewer assessments. Font color for the deficiency has been chosen red. Most of the tables have been taken from the sponsor submission and modified as needed to assist in the application evaluation.

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	Restasis® (Cyclosporine) Ophthalmic Emulsion 0.05%
Non-Proprietary Name of Drug Product	Cyclosporine Ophthalmic Emulsion 0.05%
Non-Proprietary Name of Drug Substance	Cyclosporine USP
Company Name	Mylan Pharmaceuticals Inc.
Dosage Form	Emulsion
Strength(s)	0.05%
Route of Administration	Ophthalmic
Proposed Indication(s)	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.
Maximum Daily Dose	0.06 mg/day

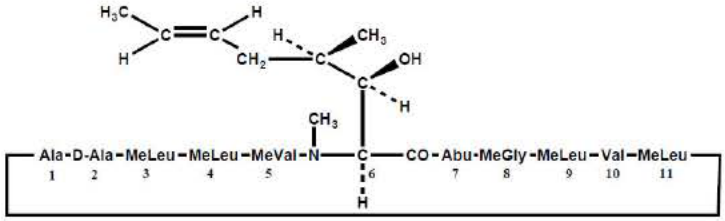
2.3.S DRUG SUBSTANCE [Cyclosporine USP]

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Firm's Response:

USAN: Cyclosporine
CAS number: 59865-13-3
Chemical Family: Immunomodulator
Molecular Formula: $C_{62}H_{111}N_{11}O_{12}$
Molecular Weight: 1202.61g/mole
Structural Formula:



11 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

2.3.P DRUG PRODUCT [Cyclosporine Ophthalmic Emulsion, 0.05%]

2.3.P.1 Description and Composition of the Drug Product

What are the components and composition of the final product? What is the function(s) of each excipient? Does any excipient exceed the IIG limit for this route of administration?

Firm's Response:

Component	0.05%			Pharmaceutical Function	IIG Limit
	Quantity (mg/mL)	% w/v	% w/w[1]		
Active Ingredient					
Cyclosporine, USP	0.500	(b) (4)		Active	-
Inactive Ingredients					
Castor Oil, NF	(b) (4)			(b) (4)	5%
Polysorbate 80, NF					(b) (4)
Glycerin USP	(b) (4)				2.2%
(Carbomer Co-polymer Type A)[4]	(b) (4)				(b) (4)
(b) (4) Sodium Hydroxide, NF[2]				pH adjusting agent	
Water for Injection, USP				(b) (4)	-
					(b) (4)

All of the excipients used in Mylan's Cyclosporine ophthalmic emulsion, 0.05% are within the limits for an ophthalmic route of administration as listed in the Inactive Ingredient Database. A comparison is summarized in the table below. The inactive ingredients do not affect the safety of the proposed drug product and the requirements outlined in 21 CFR 314.94(a)(9)(iv) have been satisfied.

Reviewer's Comment (Review #1):

The proposed product has the same formulation design and contains same amount of each component as the RLD (Restasis®). (b) (4)

(b) (4)

56 Pages have been witheld in full as b4 (CCI/TS) immediately following this page

A APPENDICES

A.1 Facilities and Equipment (biotech only): N/A

A.2 Adventitious Agents Safety Evaluation: N/A

A.3 Novel Excipients: N/A

A.4 Nanotechnology Product Information: N/A

A.5 Precedent Setting Information: N/A

R REGIONAL INFORMATION

R.1 Executed Batch Records (Refer to Sections S.4 and P.5)

R.2 Comparability Protocols

Reviewer's Assessment (Review #1):

No comparability protocol is proposed.

R.3 Methods Validation Package (Refer to Sections S.4 and P.5)

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)
Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No ☒ N/A If "No," explain.

e) For solid oral drug products, only: drug product length(s) of commercial batch(es): **N/A**

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: **N/A**

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification Provided:	☒ Yes	☐ No
Exclusivity Provided:	☒ Yes	☐ No
Debarment Certification Provided:	☒ Yes	☐ No
cGMP Statement Provided:	☒ Yes	☐ No
Reprocessing Statement Provided:	☒ Yes	☐ No
Letters of Authorization Provided:	☒ Yes	☐ No
Request for Bio-waiver Provided:	☒ Yes	☐ No

Citizen Petition and/or Control Request Linked to the Application: N/A

Environmental Impact Considerations/Categorical Exclusions Provided:	☒ Yes	☐ No

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

HFD-940/Yang, Yang, Ph.D. / Reviewer 08/20/2015; 12/18/2015; 06/14/2016; 10/21/2016
HFD-940/Ashraf, Muhammad, Ph.D. /Secondary Reviewer/10/21/2016
HFD-940/Cai, Bing, Ph.D./Tertiary Reviewer/ 11/22/16
HFD-617/Sarah Nguyen/ PM/11/22/16

TYPE OF LETTER: NOT APPROVABLE – Information request 30 days.

Bing Cai

Digitally signed by Bing Cai
Date: 11/22/2016 02:58:59PM
GUID: 508da6ff000285eddca825bf21370b48

Muhammad Ashraf

Digitally signed by Muhammad Ashraf
Date: 11/22/2016 03:16:19PM
GUID: 508da705000289defcccfe6abe65951b
Comments: Approved

Yang Yang

Digitally signed by Yang Yang
Date: 10/21/2016 01:05:50PM
GUID: 542e18bd0004452b6a70350e55371bcd

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205894Orig1sS000

BIOEQUILVANCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

COMPLETE RESPONSE AND INFORMATION REQUEST REVIEW

ANDA No.	205894		
Drug Product Name	Cyclosporine Ophthalmic Emulsion		
Strength(s)	0.05%		
Applicant Name	Mylan Pharmaceuticals Inc.		
Applicant Address	781 Chestnut Ridge Road, Morgantown, WV 26504		
US Contact Name	Wayne Talton		
US Contact Telephone Number	304-554-6551		
US Contact Fax Number	304-285-6407		
Original Submission Date	11/01/2013 (Original) 07/10/2015 (Additional BE data submitted by the firm) 02/08/2017 (Response to CR)07/06/2017 (Submission of SAS files for GSD study) 09/26/2017 (Response to IR) 06/29/2018 (Response to CR) 07/10/2019 (Response to IR about updated formulation table)		
Submission Dates of Amendments Under Review	12/17/2020 (Response to CR) 01/21/2021 (Response to First Bioequivalence IR about submission of globule-size distribution [GSD] data) 02/23/2021 (Response to Second Bioequivalence IR about submission of GSD data with revised refractive index value) 04/01/2021 (Response to Third Bioequivalence IR about submission of GSD data in a revised data structure)		
Primary Reviewer	Krishna Chimalakonda, Ph.D.		
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.		
Tertiary Reviewer	April C. Braddy, Ph.D., RAC		
First Generic	Yes		
Study Number(s)	CPSFDA-2020-02-03	CPSFDA-2020-04	CPSFDA-2020-06
Study Type(s)	Comparative Physicochemical Characterization	Comparative In Vitro Drug Release Testing	Determination of Globule Size Distribution
Strength(s)	0.05%		
Analytical Site	Mylan Laboratories Clinical Research Center		
Analytical Site Address	Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India		

Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent)	**Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)
Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ Not applicable	
Formulation	☒Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A	
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is adequate)	
Major Deficiency Theme	N/A	
Justification for Major Designation	N/A	
Overall Review Result	☒ Adequate ☐ Inadequate	
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: 10/2016 RLD Number: NDA 050790 ☐ N/A (no PSG available at time of review)	
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO	

Bioequivalence study tracking/supporting document #[1]	**Study/test type**	**Strength**	**Review Result**
1, 13, 45, 49	**Formulation Q1/Q2**	**0.05%**	☒ Adequate ☐ Inadequate
1, 13, 31, 45, 47, 49	**Globule Size Distribution**	**0.05%**	☒ Adequate ☐ Inadequate
1, 13, 31, 34, 35, 45, 49	**In vitro Release Testing**	**0.05%**	☒ Adequate ☐ Inadequate

[1] Globule-Size Distribution (GSD) and In vitro Release Testing (IVRT) studies are reviewed by Div. of Bioequivalence. The remaining studies listed in the draft product specific guidance (PSG) for Cyclosporine are reviewed by the Office of Pharmaceutical Quality (OPQ).

1 EXECUTIVE SUMMARY

This is a bioequivalence (BE) assessment of the applicant's response, dated December 17, 2020, to the complete response letter (CRL) dated Sep 20, 2020[2] and responses, dated January 21, February 23, and April 1, 2021, to the BE information requests (IR) dated January 15, February 19, and March 25, 2021[3], respectively.

In response to the CRL, the applicant reformulated the proposed test product to be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) product. The formulation of the reformulated test product is now adequate.

The applicant submitted pivotal in vitro drug-release testing (IVRT) and globule-size distribution (GSD) data, each of which used 3 lots of the reformulated test and 3 lots of the RLD products. The applicant used validated IVRT and GSD methods which were deemed adequate based on previous BE and ORS consult response assessments from 2017[4]Error! Bookmark not defined.. The pivotal IVRT data demonstrates that the test product has a similar drug release profile (f_2 >50) when compared to the RLD. The statistical analysis using earth mover distance (EMD) method followed by population bioequivalence (PBE) analysis of the pivotal GSD data demonstrates that the test product has equivalent globule size distribution profile when compared to the RLD. The pivotal IVRT and GSD data are adequate.

Per GDRP, the Office of Scientific Integrity and Surveillance (OSIS) inspection status of the current ANDA is complete[5]. The Division of Generic Drug Study Integrity (DGDSI) within the OSIS determined that an inspection is not warranted at this time as OSIS inspected the site in October 2019, which falls within the surveillance interval.

The applicant submitted threshold analyses comparing the user interface of test and reference products, as well as high-resolution color photos of each size and strength of the proposed product and each corresponding size and strength of the RLD, which were reviewed by the Division of Clinical Review (DCR) in Office of Safety and Clinical Evaluation (OSCE)[6]. DCR concluded that test product drug delivery device user interface is acceptable. DCR's conclusion is supportive of a demonstration of BE.

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[2] GDRP-ANDA-205894-Orig-1-Amend-39, Complete Response Letter, 09/30/2020 https://panorama.fda.gov/task/view?ID=5b3b75cc0012ddc28789b14999bec911

[3] GDRP ANDA 205894-Orig-1-Amend-49, 01/15/2021, 02/21/2021, and 03/25/2021. https://panorama.fda.gov/task/view?ID=5fe10e3d008c9fde027a012560156a62

[4] GDRP ANDA 205894-Orig-1-Amend-31, Bioequivalence amendment review and ORS Consult response review, Krishna Chimalakonda, 9/20/2017 https://panorama.fda.gov/task/view?ID=589e26ac00a52c5d7aa2620aa12f9b81

[5] GDRP ANDA 205894-Orig-1-Amend-49, Kimberly Miler, 03/04/2021 https://panorama.fda.gov/project/view?ID=5fdce29b0087cc2d523ff1e411a38acb

[6] GDRP for ANDA 205894-ORIG-1-AMEND-49 Combination Product Comparative Analyses Review; https://panorama.fda.gov/task/view?ID=61698b07008384cd482e08f568fc15f8, Uploaded by William Chong on Jan 28, 2022

Overall, the Division of Bioequivalence III (DBIII) accepts the applicant's approach for establishing bioequivalence in accordance with 21 CFR 320.24(b)(6).

The BE portion of the application is **adequate**.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug product Information, PK/PD Information, and Relevant DB History

The PK/PD information reflected in the RLD labeling has not been revised since the referenced review[7].

There are no approved ANDAs per Orange Book[8].

The draft PSG was last updated October 2016; no changes have been made as of 06/03/2021[9].

3.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
BE determination requests For Ophthalmic Emulsions	Yes	1
In Vitro Release Testing	Yes	1
Globule Size Distribution	Yes	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

[7] GDRP ANDA 205894-Orig-1, Bioequivalence Primary Review, Krishna Chimalakonda, 11/02/2016. http://panorama.fda.gov/task/view?ID=542124870034e8954709b1d5fdbbfa41

[8] Orange Book Online, available at: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=050790; Last accessed 06/03/2021.

[9] Draft PSG for Cyclosporine ophthalmic emulsion, 0.05%; Recommended Jun 2013; Revised Feb 2016; Revised Oct 2016, available at: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%20050790_RV09-16.pdf

3.3 Bioequivalence Determination Request(s) For Ophthalmic Emulsions

Strengths for which BE determination is requested, if applicable	0.05%
Regulation cited?	21 CFR § 320.24 (b)(6)
Strength(s) considered for 21 CFR 320.24 (b)(6)	0.05%
Proportional to strength tested in vivo?	N/A
Is IVRT study acceptable?	Yes
Is GSD acceptable	Yes
Deem Bioequivalent?	Yes
If not then why?	N/A

3.3 Deficiency Comments

None

3.4 Recommendations

The Division of Bioequivalence III (DBIII) concludes that the information submitted by Mylan Pharmaceuticals is adequate to demonstrate that its test product, Cyclosporine Ophthalmic Emulsion, 0.05%, submitted under ANDA 205894, is bioequivalent to the RLD under Section 21 CFR § 320.24(b)(6). The information is consistent with DB's current scientific thinking on establishing bioequivalence for ophthalmic drug products. The DBIII deems the test product bioequivalent to the RLD.

3.5 Comments for Other OGD Disciplines

Discipline	Comment
None	

3.6 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
None	

4 REVIEW OF RESPONSE TO COMPLETE RESPONSE LETTER (DATED SEP 20TH, 2020)

Deficiency 1: *Based on the information currently available to the Agency and your response to the information request (IR) communicated on June 28, 2019, the formulation of your proposed test product, Cyclosporine Ophthalmic Emulsion, 0.05% is not quantitatively (Q2) the same when compared to the reference listed drug (RLD) with respect to one or more inactive ingredients. If you choose to reformulate your test product to be Q1/Q2 the same as the RLD product, you should submit in vitro data using your reformulated test product to support demonstration of bioequivalence, along with complete chemistry, manufacturing and control information for evaluation. If you believe that the in vitro data that you already submitted is relevant to a demonstration of bioequivalence of your reformulated test product, please provide a justification, including how you propose to bridge your prior data to your reformulated test product. This deficiency supersedes any prior communications regarding the acceptability of the formulation of your proposed test product, including our previous response of August 24th, 2011 to your controlled correspondence (No. 11-0183) submitted on March 4th, 2011, (and subsequent amendments on May 9th, 2011 and Aug. 4th, 2011) in which you provided formulation data, and our December 8, 2016 complete response letter.*

Applicant's response: Mylan acknowledges the Agency's comment. Taking note of the Agency's comment, Mylan had filed a general correspondence on October 16, 2020 (Sequence No. 0044) to seek the Agency's concurrence on Q2 similarity between Mylan's proposed composition and the RLD, Restasis®. As a response to Mylan's general correspondence, the Agency, on December 2, 2020, made a preliminary determination that Mylan's proposed composition 1 meets the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(9)(iv) pertaining to inactive ingredients and appears to be an acceptable revised formulation. A copy of the general correspondence and the Agency's response are enclosed in Section 1.4.4 of this submission. Accordingly, as requested by the Agency, Mylan has manufactured three exhibit batches with the revised quantitative composition (b) (4) and generated complete in-vitro characterization data per the Agency's October 2016 product specific guidance. All 3 exhibit batches of the test product were manufactured in December 2019 at a (b) (4) An executive summary report comparing the characterization study results on the three exhibit batches, with the revised composition, and three lots of the RLD (Nos. 09860, 09954, and 09966) is enclosed in Section 1.12.15 of this submission. As evident, Mylan's Cyclosporine Ophthalmic Emulsion is comparable to that of the RLD, Restasis®.

4.1 Assessor's Comments

4.1.1 Formulation of the Reformulated Test Product

In response to the CRL and as shown in **Table 1** below, the applicant reformulated the proposed test product to be Q1 and Q2 the same as the RLD product.

Per the RLD labeling, the MDD of the drug product is 2 drops per eye. In the RLD labeling, one drop is assumed to be approximately equal to 28 µl. Therefore, the MDD will be 56 µl. (b) (4)

All the excipients in the proposed test product do not exceed the limit of the same inactive ingredient reflected in the Inactive Ingredient (IIG) Database for FDA approved drug products intended for the same route of administration and context of use.

Table 3.2.P.1/2: Unit Formula, Pharmaceutical Function of Components, and Quality Standards

Component	0.05%				Pharmaceutical Function	Quality Standards
	mg/g	% w/w	mg/mL	% w/v		
Active Ingredient						
Cyclosporine	(b) (4)	0.05	(b) (4)	0.05	Active	USP
Inactive Ingredients						
Castor Oil					(b) (4)	NF
Polysorbate 80						NF
Glycerin (b) (4) Anhydrous)						USP
(b) (4) (Carbomer Co-polymer Type A)						NF
Sodium Hydroxide				(b) (4)	pH adjusting agent	NF
Water for Injection					(b) (4)	USP

The formulation of the reformulated test product is **adequate**.

Table 1. Comparison of the Reformulated Test Product to the RLD and IIG Evaluation

Ingredient	Test Product %w/w (mg/g)	RLD[10] %w/w (mg/g)	% Difference [(T-R)/R*100%]	IIG limit (%w/w) based on MDD of the RLD[11]	Below or Exceed
Cyclosporine, USP	0.05	0.05	--	N/A	
Castor Oil, USP				(b) (4)	Below
Polysorbate 80, NF					Below
Glycerin, USP					Below
Carbomer Copolymer type A					Equal
Sodium Hydroxide					Below
Water for injection*					

[10] DARRTS: NDA 50790, New/Annual Report, 1/29/2016 (Module 1.13.5, p. 7). There have been no changes to the RLD composition since its approval on 12/23/2002

[11] FDA IIG database. Last accessed on 06/03/2021. https://mercado.fda.gov/analytics/saw.dll?Dashboard

(b) (4)

4.1.2 Assessment of the Pivotal In Vitro Release Testing (IVRT) Data Submitted on the Reformulated Test Product

In the current amendment dated Dec 17, 2020, the applicant submitted new pivotal in vitro drug-release testing (IVRT) data on the reformulated test product. This testing used 3 lots each, of the reformulated test and the RLD products. Also, the pivotal IVRT data was obtained from a validated rotating bottle dissolution apparatus method, and the sample analysis was conducted using a validated analytical method. The applicant previously conducted comprehensive method development and validation to identify a suitable IVRT method.[12] Prior BE reviews evaluated the IVRT method development and validation and deemed acceptable[13], based in part on ORS consult responses (and discussion with the Office of Testing and Research [OTR]) from 2017[4].

In the current submission, the applicant also submitted partial validation data of the IVRT method to demonstrate stability of Cyclosporine at room temperature (RT) for 146 hr, at 2-8 ^{0}C for 44 days and to demonstrate method precision as the run-time of the analytical method was increased from 15 min to 20 min. All validation experiments met the acceptance criteria for accuracy (within 85-115%) and precision (CV ≤15%).

4.1.3 Evaluation of the Analytical Method Precision

The precision of the analytical method for the partial validation data was evaluated by measuring drug release for up to 240 min from 6 separate IVRT experiments. The samples from this experiment were analyzed with a previously validated analytical method, however with a run time of 20 min. As seen from the table below (Table 2), drug release data are reproducible with minimal variability and are within the specified limits (CV ≤15%). This IVRT method validation data demonstrates method precision and are adequate.

[12] GDRP for ANDA-205894-ORIG-1-Amend-31, DTP Consult Response, Uploaded by Darby Kozak on Sep 18, 2017; https://panorama.fda.gov/task/view?ID=599c2ea8006c088e2c2eab11df27e723
[13] GDRP for ANDA-205894-ORIG-1-Amend-39, Bioequivalence Discipline Review, Uploaded by April Braddy on Sep 25; https://panorama fda.gov/task/view?ID=5b3b75cb0012d9076a7178dd286f1d29

Table 2. Applicant's Table of Study No.: PV (04)-136, Drug Release Data Using Reformulated Test Product

Mylan Laboratories Limited Clinical Research Center	Study No.: PV(04)-136						
	Instrument ID: CRC/BL/424						
	Analyte: Cyclosporine						
	Sequence ID: Method Precision_041219						
	B.NO: 97622 (1 TO 6 UNITS) %drug release data						
SAMMPLE ID	5 MIN	10 MIN	30 MIN	60 MIN	120 MIN	180 MIN	240 MIN
97622-U01	(b) (4)						
97622-U02							
97622-U03							
97622-U04							
97622-U05							
97622-U06							
Average	16.58	23.28	46.85	63.43	84.10	92.62	99.03
SD	0.8134	1.7011	3.6121	3.1033	2.9920	1.6582	1.6269
%CV	4.88	7.31	7.71	4.89	3.56	1.79	1.64

4.1.4 Evaluation of the Pivotal IVRT Data

In the current amendment dated 12/17/2020, the applicant submitted pivotal IVRT data using 3 lots, each, of the reformulated test (Nos. MY0A02, MY0A03, and MY0A04) and the RLD products (Nos. 09860, 09954, and 09966). The same IVRT method, used in the previous submission[4], was used by the applicant in the current submission, as shown below in Table 11 from the applicant.

Table 11. Final *in vitro* release test parameters

Product	Cyclosporine Ophthalmic emulsion
Apparatus	Bottle rotating
Dissolution medium and volume	Isobutyl acetate, 3 mL
Rotation speed	75 RPM
Sample amount	1 g (=1ml)
Temperature	37 °C
Sampling Time point	5, 10, 30, 60, 120, 180 and 240 min.
Sampling volume	0.1 mL

(b) (4)

Sample analysis during the pivotal IVRT Study

Sample analysis was conducted using a validated high-performance liquid chromatography (HPLC) method. There were no samples that were reanalyzed. The applicant submitted 100% analytical raw data. As shown in the tables below, all the analytical runs are within the acceptance criteria for accuracy (within 85-115%) and precision (CV ≤15%).

Table 3. Overview of Pivotal IVRT Study

Parameter	Results		Table No.
Total Number of Analytical runs	Six (6) acceptable analytical runs		1
Regression Coefficient (r^2)	≥ 0.99783		
Calibration	Precision (% CV)	Accuracy (% Nom)	2
	0.56% to 4.02%	97.69% to 103.09%	
Quality Control	Precision (% CV)	Accuracy (% Nom)	3
	1.45% to 4.50%	101.87% to 104.56%	
• There were no rejected runs			

(b) (4)

[redacted]

Following this page, 1 Page Withheld in Full as (b)(4)

Comparative Pivotal IVRT Data between the Reformulated Test and RLD Products

- Based on the data submitted in the IVRT method development and validation reports[4],[12], [13] rotating bottle dissolution apparatus is suitable to evaluate the comparative in vitro release testing of the reformulated test product and the RLD.

- To capture early and complete drug release from the reformulated test product and the RLD, the firm determined drug release at both early and later time points (from 5 min through 240 min).

- DBIII concluded in a previous BE assessment[13] that the IVRT method is discriminatory and captures the gradual drug release from the test product and the RLD. The applicant did not propose any changes and used previously accepted method for conducting IVRT studies comparing the re-formulated test product with the RLD product. Based on the data submitted in the current amendment, the IVRT method is considered suitable for re-formulated test product.

- The firm calculated cumulative percentage drug release *vs*. time for 3 batches each of the reformulated test product and RLD and compared the drug release profiles by calculating the f_2 value. Demonstrating similarity in drug release profile between the reformulated test product and RLD is in agreement with the consult response from ORS[4Error! Bookmark not defined.]. The applicant submitted % drug-release data using corrected and un-corrected data. Based on the applicant's response to the IR (dated Feb 23, 2021), it appears that the applicant is not correcting for drug loss but is calculating cumulative % drug-release at each time-point. Nonetheless, the uncorrected data from the pivotal IVRT data shows (b) (4)% drug-release at 240 min from all 3 lots of the reformulated test and RLD products and is considered acceptable.

- The assessor calculated the f2 value using the uncorrected and corrected IVRT data. Based on the uncorrected IVRT data presented in **Table 4**, the drug release profile is similar (f_2 value>50) between all three batches of the test and RLD products.

- Based on the corrected IVRT data shown in **Table 4**, with the exception of the f2 value between reformulated test product lot # MY0A02 Vs RLD lot # 09860, the drug release profile is similar (f_2 value>50) between all other batches of the reformulated test and RLD products. The f2 value between reformulated test product lot # MY0A02 Vs RLD lot # 09860 is slightly lower than 50 (49.3) due to slower drug-release from the RLD and is acceptable as the f2 value between test product lot # MY0A02 and the other 2 batches of the RLD product are >50 and based on uncorrected data, the f2 value between test product lot # MY0A02 Vs RLD lot # 09860 is >50.

- (b) (4)

- Previous BE assessments of submissions from 2017[4] and 2018[13] that assessed the non-Q2 test product found that the globule size was similar between the test and RLD products (b) (4) (b) (4) at all time-points over the duration of the IVRT study. This demonstrated that the proposed IVRT method is measuring Cyclosporine release from the formulation and is not a measure of formulation solubility in the release media. Consequently, globule size could not be measured (b) (4) from the test and RLD products. In summary, based on the data submitted by the applicant, the proposed IVRT method is measuring Cyclosporine release from the formulation and is not a measure of formulation solubility in the release media. The change (b) (4) between the original test formulation (which was not Q2 the same as the RLD (b) (4) and re-formulated test product (which is Q1/Q2 same as the RLD), does not alter the above conclusions that IVRT method is measuring the cyclosporine released from the formulation (b) (4) (b) (4) (b) (4)

- The applicant previously submitted supportive mass balance data (b) (4) (b) (4).[13] In the applicant's December 20, 2020 response to the complete response letter, the applicant did not submit supportive mass balance data (b) (4) This is acceptable. This information need not be resubmitted. The mass balance data of (b) (4) is not considered pivotal BE data and is only considered supportive data.

- The pivotal IVRT testing is **adequate**.

Table 4. Assessor Calculation of the f2 Value between the Test and RLD Products

Table 4. Assessor calculated f2 value between 3 Lots of the test and RLD products			
Test product lot #	**RLD lot #**	**f2 value (corrected)**	**f2 value (un-corrected)**
MY0A02	09860	49.3	50.2
	09954	55.9	56.7
	0996	62.3	62.4
MY0A03	09860	52.5	53.4
	09954	59.1	59.6
	0996	65	64.9
MY0A04	09860	86.9	86.5
	09954	80.9	76.6
	0996	66.7	68.2
MY0A02	MY0A03 (Test product)	72.1	71.8
	MY0A04 (Test product)	51.9	52.7

Table 5. Study No. CPS(FDA)-2020-004

Mylan Laboratories Limited Clinical Research Center	Study No.: CPS(FDA)-2020-004						
	Instrument ID: CRC/BL/424						
	Analyte: Cyclosporine						
	B.NO:MY0A02(1 TO 12 UNITS) %drug release data						
SAMMPLE ID	**5 MIN**	**10 MIN**	**30 MIN**	**60 MIN**	**120 MIN**	**180 MIN**	**240 MIN**
T-MY0A02-U01							(b) (4)
T-MY0A02-U02							
T-MY0A02-U03							
T-MY0A02-U04							
T-MY0A02-U05							
T-MY0A02-U06							
T-MY0A02-U07							
T-MY0A02-U08							
T-MY0A02-U09							
T-MY0A02-U10							
T-MY0A02-U11							
T-MY0A02-U12							
Average	16.433	27.283	53.600	76.675	92.717	98.108	101.683
SD	0.5087	0.8277	1.6684	1.5598	1.0760	0.5384	0.6147
%CV	3.10	3.03	3.11	2.03	1.16	0.55	0.60

Mylan Laboratories Limited Clinical Research Center	Study No.: CPS(FDA)-2020-004						
	Instrument ID: CRC/BL/424						
	Analyte: Cyclosporine						
	B.NO:MY0A03(1 TO 12 UNITS) %drug release data						
SAMMPLE ID	5 MIN	10 MIN	30 MIN	60 MIN	120 MIN	180 MIN	240 MIN
T-MY0A03-U01	(b) (4)						
T-MY0A03-U02							
T-MY0A03-U03							
T-MY0A03-U04							
T-MY0A03-U05							
T-MY0A03-U06							
T-MY0A03-U07							
T-MY0A03-U08							
T-MY0A03-U09							
T-MY0A03-U10							
T-MY0A03-U11							
T-MY0A03-U12							
Average	17.025	24.883	47.658	74.600	96.617	105.300	107.833
SD	0.4634	0.4970	1.4145	2.0190	0.8111	1.2173	0.9680
%CV	2.72	2.00	2.97	2.71	0.84	1.16	0.90

Mylan Laboratories Limited Clinical Research Center	Study No.: CPS(FDA)-2020-004						
	Instrument ID: CRC/BL/424						
	Analyte: Cyclosporine						
	B.NO:MY0A04(1 TO 12 UNITS) %drug release data						
SAMMPLE ID	5 MIN	10 MIN	30 MIN	60 MIN	120 MIN	180 MIN	240 MIN
T-MY0A04-U01	(b) (4)						
T-MY0A04-U02							
T-MY0A04-U03							
T-MY0A04-U04							
T-MY0A04-U05							
T-MY0A04-U06							
T-MY0A04-U07							
T-MY0A04-U08							
T-MY0A04-U09							
T-MY0A04-U10							
T-MY0A04-U11							
T-MY0A04-U12							
Average	16.167	23.333	41.967	61.675	86.500	100.058	104.942
SD	0.3393	0.4579	1.1130	1.8076	2.1713	1.8033	1.1603
%CV	2.10	1.96	2.65	2.93	2.51	1.80	1.11

Mylan Laboratories Limited Clinical Research Center	Study No.: CPS(FDA)-2020-004						
	Instrument ID: CRC/BL/424						
	Analyte: Cyclosporine						
	B.NO:09860(1 TO 12 UNITS) %drug release data						
SAMMPLE ID	5 MIN	10 MIN	30 MIN	60 MIN	120 MIN	180 MIN	240 MIN
R-09860-U01	(b) (4)						
R-09860-U02							
R-09860-U03							
R-09860-U04							
R-09860-U05							
R-09860-U06							
R-09860-U07							
R-09860-U08							
R-09860-U09							
R-09860-U10							
R-09860-U11							
R-09860-U12							
Average	14.358	21.358	40.342	60.292	85.983	97.792	102.442
SD	1.0578	0.4316	2.7606	2.7763	0.9514	1.0131	0.4602
%CV	7.37	2.02	6.84	4.60	1.11	1.04	0.45

Mylan Laboratories Limited Clinical Research Center	Study No.: CPS(FDA)-2020-004						
	Instrument ID: CRC/BL/424						
	Analyte: Cyclosporine						
	B.NO:09954(1 TO 12 UNITS) %drug release data						
SAMMPLE ID	5 MIN	10 MIN	30 MIN	60 MIN	120 MIN	180 MIN	240 MIN
R-09954-U01	(b) (4)						
R-09954-U02							
R-09954-U03							
R-09954-U04							
R-09954-U05							
R-09954-U06							
R-09954-U07							
R-09954-U08							
R-09954-U09							
R-09954-U10							
R-09954-U11							
R-09954-U12							
Average	18.150	25.292	43.133	65.525	86.275	95.517	100.500
SD	0.3477	0.3528	0.3676	0.3745	0.4883	0.6103	0.6208
%CV	1.92	1.39	0.85	0.57	0.57	0.64	0.62

Mylan Laboratories Limited Clinical Research Center	Study No.: CPS(FDA)-2020-004 Instrument ID: CRC/BL/424 Analyte: Cyclosporine B.NO:09966(1 TO 12 UNITS) %drug release data						
SAMMPLE ID	5 MIN	10 MIN	30 MIN	60 MIN	120 MIN	180 MIN	240 MIN
R-09966-U01							(b) (4)
R-09966-U02							
R-09966-U03							
R-09966-U04							
R-09966-U05							
R-09966-U06							
R-09966-U07							
R-09966-U08							
R-09966-U09							
R-09966-U10							
R-09966-U11							
R-09966-U12							
Average	19.642	28.075	45.358	68.883	88.450	96.975	102.608
SD	0.5680	1.0532	0.7960	1.2261	1.8198	1.0163	0.8565
%CV	2.89	3.75	1.75	1.78	2.06	1.05	0.83

4.1.5 Assessment of the Pivotal Globule-size Distribution (GSD) Data Submitted on the Reformulated Test Product

In the applicant's December 17, 2020 response to the complete response letter, the applicant submitted pivotal globule-size distribution (GSD) data using 3 lots, each, of the reformulated test and the RLD products and using the validated DLS method used previously[Error! Bookmark not defined.] without changes or modifications. Previous BE reviews, relying in part on an ORS consult response from 2017[4], concluded that the comprehensive method validation of the GSD method using Dynamic Light Scattering (DLS) conducted by the applicant was acceptable.

In the current submission, the applicant also submitted partial validation data of the GSD method using the RLD product to demonstrate robustness of the GSD method by varying the number of measurements (either 3 or 8 measurements). The partial method validation data shows that varying the number of measurements does not have any effect on the GSD profile of the RLD product. All validation experiments met the acceptance criteria for accuracy (within 85-115%) and precision (CV ≤15%).

4.1.6 Evaluation of the Pivotal GSD Data

Pivotal GSD data was submitted, using 3 lots, each, of the reformulated test (Nos. MY0A02, MY0A03, and MY0A04) and the RLD products (Nos. 09860, 09954, and 09966). The same GSD method, used in the previous submission, was used by the applicant in the current submission, as detailed below.

GSD Method using Dynamic Light Scattering

Sixty randomized and blinded Cyclosporine Ophthalmic Emulsion 0.05% single dose vials from three lots, each of the test and the RLD products (10 vials from each lot per product) were used

to generate GSD data. [redacted] (b) (4) [redacted]. A previous BE review and ORS consult response[4] concluded that the GSD measurement at 100X dilution of the test and RLD products generates accurate GSD data with minimal noise; DBIII concludes that this conclusion remains valid for the new data.

Sample analysis during the pivotal GSD Study

1. Sample analysis was conducted using the validated DLS method.
2. Eight (8) samples were re-injected due to software communication error.
3. One analytical run was rejected due to sample processing error (presence of sedimentation particles at the bottom of the cuvette).
4. The applicant submitted 100% analytical raw data. All the acceptable analytical runs are within the acceptance criteria for accuracy (within 85-115%) and precision (CV ≤15%).

[redacted] (b) (4)

Table 6. PBE analysis based on calculated EMD distances for the reformulated test and RLD products. Applicant calculated

Variable	Sigma_T	Sigma_R	Linearized Point Estimate	95% Upper Confidence Bound	PBE Result
EMD (Reference scaled)	[redacted] (b) (4)				Pass

Table 7 Means and variances of two groups of distances (i.e., R-R vs. T-R) Applicant calculated		
Distance	**Mean**	**Variance**
Reformulated Test - RLD center	(b) (4)	
RLD - RLD center		

Table 8 PBE analysis based on calculated EMD distances for the reformulated test and RLD products. Assessor calculated					
Variable	**Sigma_T**	**Sigma_R**	**Linearized Point Estimate**	**95% Upper Confidence Bound**	**PBE Result**
EMD (Reference scaled)	(b) (4)				Pass
EMD/PBE analysis was conducted by Drs. Devvrat Patel from OGD/OB/DBIII and Fenggong Wang and Meng Hu from OGD/ORS/DQMM.					

Table 9 Means and variances of two groups of distances (i.e., R-R vs. T-R) Assessor calculated		
Distance	**Mean**	**%CV**
Reformulated Test - RLD center	(b) (4)	
RLD - RLD center		

1. In the current submission, the applicant submitted GSD data using the narrow mode on 3 lots, each, of the reformulated test product and the RLD using undiluted and serially diluted (25-, 50-, 100-, and 200-fold) samples. A previous BE assessment, in agreement with an ORS consult response from 2017[4] and discussion with the Office of Testing and Research [OTR], concluded that the earth mover's distance (EMD) / population bioequivalence (PBE) analysis of the GSD data should be evaluated based on the 100X diluted samples of 3 lots, each, of the test and RLD products.

2. The applicant conducted statistical analysis using the EMD /PBE method to demonstrate equivalence between the shape of the globule size distribution profiles of the reformulated test and RLD products. This approach is consistent with FDA's current scientific thinking and, if finalized as written, would be recommended by the draft product specific guidance on cyclosporine ophthalmic emulsion, 0.5%. Both the applicant's and the assessor's evaluations (see **Tables 6-9** above) using the EMD and PBE analyses support the conclusion that the reformulated test product is bioequivalent to the RLD. The EMD/PBE analysis was conducted by Drs. Devvrat Patel from OGD/OB/DBIII and Fenggong Wang and Meng Hu from OGD/ORS/DQMM and the results were included in "Section 4.5 Attachments" of this review.

3. Although the results of EMD/PBE analyses calculated by the applicant and assessor are somewhat different, statistical metric in both cases is acceptable. The results of the PBE analysis show that the upper confidence bound is less than zero (b) (4). Per FDA's current scientific thinking, an adequate profile comparison of GSD between the test product and RLD is supportive of a conclusion of bioequivalence. The difference in the results[4] is likely due to different implementation of EMD algorithm[9].

4. The pivotal GSD study is **adequate**.

4.2 Review of Applicant's Response to the First Bioequivalence Information Request (IR was communicated on Jan. 15th, 2021)

IR Language: *For your pivotal globule size distribution (GSD) study (No. CPS(FDA)-2020-005-006), please submit SAS transport files to assess the difference between the shapes of globule size distribution profile for each of the 3 lots of the test (Nos. MY0A02, MY0A03, MY0A04) and RLD (Nos. 09954, 09860, 09966) products. SAS transport files for the complete shape of the globule size distribution profile should be submitted for Agency's evaluation.*

Applicant's Response:

Response to IR.pdf

Assessor's Comment: The applicant submitted the requested pivotal GSD data in the SAS format to the Agency for evaluation. The applicant's response is adequate.

4.3 Review of Applicant's Response to the Second Bioequivalence Information Request (IR was communicated on Feb. 19th, 2021)

IR Language: *The Agency acknowledges your response to the Information request (IR) communicated on Jan 15th, 2021, regarding submission of SAS transport files for the complete shape of the globule size distribution (GSD) profile (study # CPS-2020-006). Please clarify if the GSD data (on 100X diluted samples), submitted in response to the IR, was generated using the revised refractive index (RI)* (b) (4) (b) (4) *and submit complete GSD profile data (on 100X diluted samples) in SAS transport files for Agency's evaluation.*

Applicant's Response (dated Feb 23, 2021): Mylan would like to clarify that the data submitted in the Information Request Response on January 21, 2021 (Sequence No. 0047) was generated using the RI value (b) (4) As requested by the Agency, Mylan has reprocessed that data using the RI value (b) (4). Further, as requested by the Agency, a complete GSD profile using the RI value (b) (4) in SAS transport file (Define and XPT) for each of the three (3) lots of test (Nos. MY0A02, MY0A03, MY0A04) and the RLD lots of RESTASIS® (Nos. 09954, 09860, 09966) is enclosed. Please note that a statistical summary report for GSD using the RI

value (b) (4) Report # SP-CPS(FDA)- 2020-006-Supplement-01) was submitted in the Resubmission – Major Complete Response.

Assessor's Comment: As requested, the applicant re-processed the data using the refractive index (RI) value (b) (4) and submitted the complete GSD profile data. The applicant's response is adequate.

IR Language: *For your pivotal IVRT study (No. CPS(FDA)-2020-004), you submitted % drug-release data with and without correction. Please clarify the reason for correcting the drug release data?*

Applicant's Response: As requested by the Agency, Mylan wishes to clarify the reason for correcting the drug release data. The IVRT method for evaluating Cyclosporine Ophthalmic Emulsions involves multiple sampling time points. As part of the method, 0.1 mL of aliquot is withdrawn from each centrifuge tube at every sampling time point and the equivalent volume (0.1 mL) is replaced with dissolution medium. With the replacement, the volume used in the calculations remains the same. However, there is some amount of drug withdrawn with each sample that will need to be accounted for in the calculations. The use of correction factor in the calculations corrects the amount of drug that is lost from the medium due to sampling. The correction factor adds back the amount of drug contained in each sample volume to the cumulative amount calculated at subsequent time points.

Assessor's Comment: Based on the applicant's response, it appears that the applicant is not correcting for drug loss but is calculating cumulative % drug-release at each time-point. Nonetheless, the uncorrected data from the pivotal IVRT data shows (b) (4) drug-release at 240 min from all 3 lots of the reformulated test and LRD products and is considered acceptable. The assessor also calculated the f2 value using the uncorrected IVRT data. The applicant's response is adequate. The pivotal IVRT study is adequate for the reasons discussed throughout this review.

4.4 Review of Applicant's Response to the Third Bioequivalence Information Request (IR was communicated on March 25th, 2021)

IR Language: *In your pivotal globule size distribution (GSD) study, you determined GSD profile (after 100-fold dilution) from 3 lots, 10 vials/lot, 4 preparations (or aliquots), and 8 measurements (or replicates), each of the test and reference listed drug (RLD) products [or 3 lots x 10 vials x 4 aliquots x 8 replicates] and subsequently calculated earth-mover distance (EMD) and conducted statistical analysis of the EMD data using population bioequivalence (PBE) analysis. The data format for PBE analysis usually follows "lot x vial x replicate". From a statistical perspective, please clarify the following:*

- *Please clarify why you have the "replicate" component in addition to "aliquot"?*
- *Please clarify if "aliquot" is treated similar to "replicate"?*

- *Please submit GSD profile data (from 100-fold diluted samples using refractive index of (b) (4) in the following format: "lot x vial x replicate". In addition, please submit the SAS/R code.*
- *Please clarify if averaging or pooling of EMD data from the aliquots or replicates was conducted in the statistical analysis?*

Applicant's Response:

Response to Third IR.pdf

Assessor's Comments:

Please clarify why you have the "replicate" component in addition to "aliquot"?

The applicant stated that the "purpose of having multiple replicates (globule size measurements) [from each aliquot] provides the ability to evaluate the size measurements variability and to better estimate the size variability of the same samples (each aliquot) when analyzed using zetasizer. Statistically, a larger number of replicate measurements will result in a more accurate variability estimate than a smaller number of replicate measurements."

Please clarify if "aliquot" is treated similar to "replicate"?

The applicant stated that the "intent of preparing multiple aliquots is to evaluate the sample preparation (within vial) variability at 100X dilution from the same vial and the intent of measuring multiple replicates is to evaluate the measurement (instrument) variability of each aliquot on the same sample analyzed using the (b) (4) zetasizer." In summary, the applicant stated that "aliquot (sample preparation number) and replicates (globule size measurements) are two different entities and both are sources of variability." The variances from these sources were used in the statistical analysis.

Please submit GSD profile data (from 100-fold diluted samples using refractive index (b) (4)) in the following format: "lot x vial x replicate". In addition, please submit the SAS/R code.

As requested, the applicant submitted the GSD profile data (from 100-fold diluted samples using refractive index (b) (4)) in the requested format: "lot x vial x replicate" along with the SAS code.

Please clarify if averaging or pooling of EMD data from the aliquots or replicates was conducted in the statistical analysis?

The applicant stated that "the eight (8) replicates were averaged to produce four (4) aliquot EMDs. These four (4) aliquot EMDs were then utilized as the inputs to the population bioequivalence analysis in order to estimate the within unit variance component due to aliquot and all other mean/variance components…"

The applicant's responses are adequate.

4.5 Attachments

	Results	Code
EMD/PBE analysis	results0520.xlsx	calcemd_pbe3.R PBE4emd_6rep.R main2.R
The EMD/PBE analysis was conducted by Drs. Devvrat Patel from OGD/OB/DBIII and Fenggong Wang and Meng Hu from OGD/ORS/DQMM on May 20, 2021		

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA	205894
APPLICANT	Mylan Pharmaceuticals
DRUG PRODUCT	Cyclosporine Ophthalmic Emulsion, 0.05%

The Division of Bioequivalence III (DBIII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	205894		
Drug Product Name	Cyclosporine Ophthalmic Emulsion		
Strength(s)	0.05%		
Applicant Name	Mylan Pharmaceuticals		
Applicant Address	781 Chestnut Ridge Road, Morgantown, WV 26504		
US Contact Name	Wayne Talton		
US Contact Telephone Number	304-554-6551		
US Contact Fax Number	304-285-6407		
Original Submission Date	11/01/2013		
Submission Dates of Amendments Under Review	10/16/2020 (General correspondence requesting input on acceptability of the revised formulation of the test product from a Q1/Q2 perspective)		
Primary Reviewer	Krishna Chimalakonda, Ph.D.		
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.		
Tertiary Reviewer	April C. Braddy, Ph.D., RAC		
First Generic	Yes		
Study Number(s)	CPS-CRT	CPS-CRT-00	CPS-IVR-Part IV
Study Type(s)	Comparative Physicochemical Characterization	Determination of Globule Size Distribution	Comparative In Vitro Drug Release Testing
Strength(s)	0.05%		
Analytical Site	Mylan Laboratories Clinical Research Center		
Analytical Site Address	Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	
Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**		
QC Dissolution	☐ **Pending** ☐ **Adequate** ☐ **Inadequate** ☒ **Not applicable**		
Formulation	☐**Adequate** ☒ **Inadequate**		

Will Response to CR Result in a Reformulation?	☒ Possibly ☐ No ☐ N/A		
Deficiency Classification	☒ Major/CR ☐ Minor ☐ N/A		
Major Deficiency Theme	Formulation and New BE studies.		
Justification for Major Designation	The bioequivalence deficiency sent in a CRL on September 30, 2020was classified as MAJOR because the deficiency pertains to inadequate formulation (i.e., new BE data is requested after reformulating the test product). See, e.g., in Appendix A, Section B.1.a of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018) (describing examples of major amendments). The review of the response to the CRL will require, in FDA's judgment, a substantial expenditure of FDA resources.		
Overall Review Status of ANDA	☐ Adequate ☒ Inadequate[1]		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: 10/2016 RLD Number: NDA 050790 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #[2]	**Study/test type**	**Strength**	**Summary of Prior ANDA Review Results**
1, 13, 45, 46	Formulation Q1/Q2	0.05%	☐ Adequate ☒ Inadequate
1, 13, 31	Globule Size Distribution	0.05%	☐ Adequate ☒ Inadequate[3]
1, 13, 31, 34, 35, 45	In vitro Release Testing	0.05%	☐ Adequate ☒ Inadequate[4]

[1] In FDA's January 2, 2018 response to the citizen petition submitted in Docket No. FDA-2017-P-4745, FDA stated that the petitioner's requests that implicate the nature of the data and information necessary to support approval of an ANDA for cyclosporine ophthalmic emulsion will be considered in the context of our review of the specific ANDAs. The review of this ANDA identified deficiencies in the application resulting in a complete response letter. Complete response letters do not constitute final agency action, as they are not the end of the decision-making process for the agency. As such, the complete response is not intended to be a final decision on any such issues.

[2] Globule-Size Distribution (GSD) and In vitro Release Testing (IVRT) studies are reviewed by Div. of Bioequivalence. The remaining studies listed in the draft product specific guidance (PSG) for Cyclosporine are reviewed by the Office of Pharmaceutical Quality (OPQ).

[3] Due to the formulation being inadequate, the results of this study are inadequate to support a determination of bioequivalence between the test and reference products. However, the design, conduct and results from the study demonstrate comparability for the formulation that was tested and the reference product.

[4] Due to the formulation being inadequate, the results of this study are inadequate to support a determination of bioequivalence between the test and reference products. However, the design, conduct and results from the study demonstrate comparability for the formulation that was tested and the reference product.

1 EXECUTIVE SUMMARY

This is a review of the general correspondence dated 10/16/2020.

The applicant is currently requesting guidance as to whether the three proposed compositions of their proposed test product, Cyclosporine Ophthalmic Emulsion, 0.05% are qualitatively and quantitatively (Q1/Q2) the same when compared to the reference listed drug (RLD) product, Restasis® (cyclosporine) Ophthalmic Emulsion, 0.05%. The applicant submitted three formulation compositions. The applicant's correspondence is in response[5] to the complete response letter (CRL)[6] where it was communicated to the applicant that the formulation of their proposed test product, Cyclosporine Ophthalmic Emulsion, 0.05% is not Q1/Q2 the same when compared to the RLD and that the applicant should reformulate the test product and submit in vitro data using the reformulated test product to support demonstration of bioequivalence.

Based on the data submitted in the current general correspondence, the proposed composition 1 of the test product (identified by Mylan as its preferred composition) is Q1/Q2 the same when compared to the RLD, while compositions 2 and 3 are not Q2 the same. In addition, based on the maximum daily dose (MDD) of the RLD product, all the excipients in the proposed test products do not exceed the limit of the same inactive ingredient reflected in the Inactive Ingredient Database for FDA-approved drug products intended for the same route of administration and context of use.

It will be communicated to the applicant that the proposed composition 1 of the test product preliminarily appears to meet the applicable requirements[7] regarding inactive ingredients and to be adequate to respond to the bioequivalence deficiency in the CRL. Data to support that the new formulation is bioequivalent to the RLD will need to be provided and reviewed in the response to the CRL.

This General Correspondence does not fully address the deficiency outlined in the CRL (i.e., no data to support that any of the proposed formulations is bioequivalent are submitted). The overall assessment of the application remains **inadequate**.

[5] Lorenz docubridge, sequence 48, 10/16/2020, General correspondence
[6] GDRP-ANDA-205894-Orig-1-Amend-48, complete response letter, 09/30/2020 https://panorama.fda.gov/task/view?ID=5b3b75cc0012ddc28789b14999bec911
[7] 21 CFR 314.94(a)(9)(iv)

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3 REVIEW OF GENERAL CORRESPONDENCE

3.1 Applicant's General Correspondence dated 10/16/2020

The following italicized text and charts are an excerpt from the Applicant's General Correspondence dated 10/16/2020 (with highlighting added by FDA):

As recommended by FDA, the purpose of this General Correspondence is to seek the Agency's concurrence on Q1/Q2 similarity of its proposed compositions for Cyclosporine Ophthalmic Emulsion, 0.05% against the RLD Restasis®. While we have presented three alternate formulations in this General Correspondence for assessment by the Agency, please note that Composition 1 (Table 1) represents the preferred composition that Mylan previously presented to FDA, along with supportive data, during the Scientific Discussion Meeting held with the Agency on October 25, 2019. We wish to emphasize that, should Composition 1 be confirmed acceptable, Mylan intends to promptly respond the September 30, 2020 CRL with updated CMC information and characterization data, as Mylan has already manufactured exhibit batches consistent with Composition 1 and has generated all the relevant data. If more than one composition presented in Tables 1 and 2 is acceptable to the Agency, we would also request that the Agency advise us accordingly, which has been standard practice in previous Q1/Q2 Controlled Correspondences. If none of these three compositions are considered acceptable, Mylan also requests that the Agency provide clarity on which component is of concern.

Mylan's proposed compositions are provided below in Tables 1 and 2.

Table 1: Mylan's Preferred Composition
(same as presented in the Scientific Discussion Meeting held on October 25, 2019)

Ingredients	Function in Mylan's Product	Composition 1			
		mg/g	%w/w	mg/mL*	%w/v
Cyclosporine USP	Active Ingredient	(b) (4)	0.05	(b) (4)	0.05
Castor Oil USNF		(b) (4)			
Glycerin USP					
Polysorbate 80 USNF					
Carbomer Copolymer Type A, (b) (4)					
Sodium Hydroxide USNF	pH Adjusting Agent	(b) (4)			
Water for Injection USP	(b) (4)				
(b) (4)					

Table 2: Mylan's Alternate Compositions

Ingredients	Function in Mylan's Product	Composition 2				Composition 3			
		mg/g	% w/w	mg/mL*	% w/v	mg/g	% w/w	mg/mL*	% w/v
(b) (4)									

Mylan is respectfully requesting an expedited review of this General Correspondence so that we can timely respond to the September 30, 2020 CRL and bring this important first generic product to the market on the earliest date possible.

3.2 Assessor's Comments on the General Correspondence

- In the CRL dated September 30, 2020[6], it was communicated to the applicant that the formulation of their proposed test product, Cyclosporine Ophthalmic Emulsion, 0.05% is not Q1/Q2 the same when compared to the RLD product with respect to one or more inactive ingredients.
- In response to the CRL, on Oct 16th, 2020[5], the applicant submitted a general correspondence requesting guidance from a Q1/Q2 similarity perspective on three proposed compositions of the test product (composition 1, 2, and 3, as listed in page #02 of the General correspondence).
- Based on the data submitted by the applicant and based on Tables 3-4 (generated by the Bioequivalence reviewer) below, the proposed composition 1 of the test product (or applicant's preferred composition) is Q1/Q2 the same when compared to the RLD while compositions 2 and 3 are not Q2 the same (b) (4).
- (b) (4)
- In addition, based on the maximum daily dose (MDD) of the RLD product, all the excipients in the proposed test product do not exceed the limit reflected in the Inactive Ingredient Database of the same inactive ingredient for previously FDA-approved drug products intended for the same route of administration and context of use.
- It will be communicated to the applicant that OGD has made a preliminary determination that the proposed composition 1 of the test product formulation meets the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(9)(iv) pertaining to inactive ingredients and that it appears to be an acceptable formulation to respond to the product formulation portion of the bioequivalence deficiency in the CRL. Data to support that the new formulation is bioequivalent to the RLD will need to be provided and reviewed in the response to the CRL.
- This General Correspondence does not fully address the deficiency outlined in the CRL (i.e., no data to support that any of the proposed formulations is bioequivalent are submitted). The overall assessment of the application remains **inadequate**.

Table 3: Comparison of the Revised Formulation of the Test product with the RLD Formulation

Ingredient	Test Product Composition 1	RLD[8]	% Diff. [(T-R)/ R*100%]	IIG limit (%w/w) based on MDD of the RLD	Below or Exceed
	%w/w	%w/w			
Cyclosporine, USP	0.05	0.05	--	N/A	
Castor Oil, USP				(b) (4)	Below
Polysorbate 80, NF					Below

[8] DARRTS: NDA 50790, New/Annual Report, 1/29/2016 (Module 1.13.5, p. 7). There are no changes to the RLD composition since its approval on 12/23/2002

Glycerin, USP		(b) (4)	Below
Carbomer Copolymer type A			Equal
Sodium Hydroxide			Below
Water for injection*			

(b) (4)

Table 4: Comparison of the Revised Formulation of the Test product with the RLD Formulation

Ingredient	Test Product Composition 2 %w/w	% Diff. [(T-R)/ R*100%]	Test Product Composition 3 %w/w	% Diff. [(T-R)/ R*100%]	RLD[8] %w/w
(b) (4)					

4 DEFICIENCY COMMENT

The application remains inadequate, pending response to the CRL.

5 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
N/A	

6 ATTACHMENTS

General correspondence dated 10/16/2020	General Correspondence.pd

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA:	205894
APPLICANT:	Mylan Pharmaceuticals
DRUG PRODUCT:	Cyclosporine Ophthalmic Emulsion, 0.05%

The Division of Bioequivalence III (DBIII) has completed its review of your general correspondence dated October 16, 2020, and has the following comment:

Based on the evaluation of the three compositions of your proposed test product, Cyclosporine Ophthalmic Emulsion, 0.05% (compositions 1, 2, and 3), the Agency has made a preliminary determination that the proposed Composition 1 meets the requirements of section 505(j) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(9)(iv) pertaining to inactive ingredients and appears to be an acceptable revised formulation to address the Bioequivalence deficiency related to your product formulation outlined in the Complete Response Letter dated September 30, 2020. Consistent with the June 28, 2019 Information Request, you should list the specific amount of each inactive ingredient, including water, in the Components and Composition table. Compositions 2 and 3 are not preliminarily considered to meet the requirements of section 505(j) and 314.94(a)(9)(iv).

We remind you that you should submit in vitro data using your reformulated test product to support demonstration of bioequivalence, along with complete chemistry, manufacturing and control information for evaluation.

Sincerely yours,

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 205894
Completed Assignment for 205894 ID: 43671

Reviewer:	Chimalakonda, Krishna	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:			

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Sc re*	*Subt al*
43671	10/16/2020	BIO	ANDA Amendment [1]	1	1
43671	10/16/2020	Para lel	Minor Amendment (Original or Supplement) [1]		1
				Total	2

DIVISION OF BIOEQUIVALENCE REVIEW

COMPLETE RESPONSE AND INFORMATION REQUEST REVIEW

ANDA No.	205894		
Drug Product Name	Cyclosporine Ophthalmic Emulsion		
Strength(s)	0.05%		
Applicant Name	Mylan Pharmaceuticals		
Applicant Address	781 Chestnut Ridge Road, Morgantown, WV 26504		
US Contact Name	Wayne Talton		
US Contact Telephone Number	304-554-6551		
US Contact Fax Number	304-285-6407		
Original Submission Date	11/01/2013		
Submission Dates of Amendments Under Review	6/29/2018 (Response to CR) 7/10/2019 (Response to Bioequivalence IR about updated formulation table)		
Primary Reviewer	Krishna Chimalakonda, Ph.D.		
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.		
Tertiary Reviewer	April C. Braddy, Ph.D., RAC		
First Generic	Yes		
Study Number(s)	CPS-CRT	CPS-CRT-00	CPS-IVR-Part IV
Study Type(s)	Comparative Physicochemical Characterization	Determination of Globule Size Distribution	Comparative In Vitro Drug Release Testing
Strength(s)	0.05%		
Analytical Site	Mylan Laboratories Clinical Research Center		
Analytical Site Address	Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)**	
Deem Bioequivalent	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**		
QC Dissolution	☐ **Pending** ☐ **Adequate** ☐ **Inadequate** ☒ **Not applicable**		

Formulation	☐Adequate ☒ Inadequate		
Will Response to CR Result in a Reformulation?	☒ Possibly ☐ No ☐ N/A		
Deficiency Classification	☒ Major/CR ☐ Minor ☐ N/A		
Major Deficiency Theme	Formulation and New BE studies.		
Justification for Major Designation	The bioequivalence deficiency has been classified as MAJOR because the deficiency pertains to inadequate formulation (i.e., new BE data is requested after reformulating the test product). See, e.g., in Appendix A, Section B.1.a of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018) (describing examples of major amendments). The review of the response will require, in FDA's judgment, a substantial expenditure of FDA resources.		
Overall Review Result	☐ Adequate ☒ Inadequate[1]		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: 10/2016 RLD Number: NDA 050790 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #[2]	**Study/test type**	**Strength**	**Review Result**
1, 13, 45, 46	Formulation Q1/Q2	0.05%	☐ Adequate ☒ Inadequate
1, 13, 31	Globule Size Distribution	0.05%	☐ Adequate ☒ Inadequate[3]

[1] In FDA's January 2, 2018 response to the citizen petition submitted in Docket No. FDA-2017-P-4745, FDA stated that the petitioner's requests that implicate the nature of the data and information necessary to support approval of an ANDA for cyclosporine ophthalmic emulsion will be considered in the context of our review of the specific ANDAs. The current review has identified deficiencies in the application resulting in a complete response letter. Complete response letters do not constitute final agency action, as they are not the end of the decision-making process for the agency. As such, the complete response is not intended to be a final decision on any such issues.

[2] Globule-Size Distribution (GSD) and In vitro Release Testing (IVRT) studies are reviewed by Div. of Bioequivalence. The remaining studies listed in the draft product specific guidance (PSG) for Cyclosporine are reviewed by the Office of Pharmaceutical Quality (OPQ).

[3] Due to the formulation being inadequate, the results of this study are inadequate to support a determination of bioequivalence between the test and reference products. However, the design, conduct and results from the study demonstrate comparability for the formulation that was tested and the reference product.

1, 13, 31, 34, 35, 45	**In vitro Release Testing**	**0.05%**	☐ **Adequate** ☒ **Inadequate**[4]

1 EXECUTIVE SUMMARY

This is a bioequivalence (BE) assessment of the applicant's response to the complete response letter (CRL) dated May 21, 2018[5] and response to the BE information request (IR) dated June 28, 2019[6].

The CRL was issued to request submission of data on the mass balance of (b) (4) (b) (4) across the duration of the *in vitro* release testing (IVRT) study. In response to the CRL, while the applicant submitted the requested data, it is still **inadequate** due to the identified deficiency related to the formulation.

In addition, in response to the IR request[6], the applicant submitted an updated components and composition table (b) (4) (b) (4) Based on the submitted information, the test product is considered Q1 but not Q2 the same when compared to the reference listed drug (RLD) (b) (4) (b) (4).

Of note, based on previous BE assessment and ORS consult response, the IVRT and Globule Size Distribution (GSD) studies were deemed adequate as the scientific acceptability of the methods are formulation independent[12,16,17]. Further evaluation of these studies will be determined after Mylan submits its response to the identified deficiency.

Per GDRP, the Office of Scientific Integrity and Surveillance (OSIS) inspection status of the current ANDA is complete[7].

Overall, the Division of Bioequivalence III (DBIII) does not accept the applicant's approach for establishing bioequivalence in accordance with 21 CFR 320.24(b)(6) due to the identified formulation deficiency.

The BE portion of the application is **inadequate** with a deficiency.

---

[4] Due to the formulation being inadequate, the results of this study are inadequate to support a determination of bioequivalence between the test and reference products. However, the design, conduct and results from the study demonstrate comparability for the formulation that was tested and the reference product.

[5] GDRP ANDA 205894-Orig-1-Amend-31, Andrew Kim, 5/21/2018. http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

[6] GDRP ANDA 205894-Orig-1-Amend-39, Sylvia Park, 6/28/2019. https://panorama.fda.gov/project/view?ID=5b3b1c00000e159503d9fc44dd46bbb3

[7] GDRP ANDA 205894-Orig-1-Amend-31, Nicola Fenty-Stewart, 4/06/2018. last accessed date: 4/12/17

NOTE TO REGULATORY PROJECT MANAGER (RPM):
As of 26 May 2020, there is a Policy Alert regarding the current drug product, in which OGD will need to assess certain arguments related to 180-day exclusivity prior to any approval action and OGD continues to consider issues raised in several Citizen Petitions (CPs) regarding approval standards for ANDAs referencing Restasis. No Approval Actions (TA/AP) can be taken and no CRL/DRL can be issued prior to contacting Policy Lead.

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3 SUBMISSION SUMMARY

3.1 Drug product Information, PK/PD Information, and Relevant DB History

The PK/PD information has not been revised since the referenced review[8].

There are no approved ANDAs per online Orange Book[9].

There are no changes to the BE recommendations in the draft PSG as of 06/18/2020[10].

3.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
BE determination requests For Ophthalmic Emulsions	Yes	1
In Vitro Release Testing	Yes	1
Globule Size Distribution	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

3.3 Bioequivalence Determination Request(s) For Ophthalmic Emulsions

Strengths for which BE determination is requested, if applicable	0.05%
Regulation cited?	21 CFR § 320.24 (b)(6)
Strength(s) considered for 21 CFR 320.24 (b)(6)	0.05%
Proportional to strength tested in vivo?	N/A
Is IVRT study acceptable?	No[11]

[8] GDRP ANDA 205894-Orig-1, Bioequivalence Primary Review, Krishna Chimalakonda, 11/02/2016. http://panorama.fda.gov/task/view?ID=542124870034e8954709b1d5fdbbfa41

[9] Orange Book Online. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=050790; Last accessed 06/18/2020.

[10] Draft PSG for Cyclosporine ophthalmic emulsion, 0.05%; Recommended Jun 2013; Revised Feb 2016; Oct 2016 https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%20050790_RV09-16.pdf

[11] Due to the formulation being inadequate, the results of this study are inadequate to support a determination of bioequivalence between the test and reference products. However, the design, conduct

Deem Bioequivalent?	No
If not then why?	The test product is not Q2 the same when compared to the RLD.

3.3 Deficiency Comments

Please see the deficiency letter.

3.4 Recommendations

The Division of Bioequivalence III (DBIII) does not agree that the information submitted by Mylan Pharmaceuticals, demonstrates that its test product, Cyclosporine Ophthalmic Emulsion, 0.05%, meets the requirements of Section 21 CFR § 320.24(b)(6), along with the current DB recommendations for ophthalmic drug products, due to the deficiency specified in the letter. The DBIII does not deem the test product bioequivalent.

3.5 Comments for Other OGD Disciplines

Discipline	Comment
None	

3.6 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
None	

4 REVIEW OF RESPONSE TO COMPLETE RESPONSE LETTER (DATED MAY 21ST, 2018)

Deficiency Related To In Vitro Release Testing (IVRT)

Deficiency 1: *Your in vitro drug release testing (IVRT) study (No. CPS-IVR-Part IV) using the rotating bottle dissolution apparatus is inadequate. As requested previously in the IR dated Sept. 20, 2017, please provide information on mass balance of* (b) (4) (b) (4) *from your proposed test product and the reference listed drug (RLD) product; Restasis®, over the complete duration of the IVRT study.*

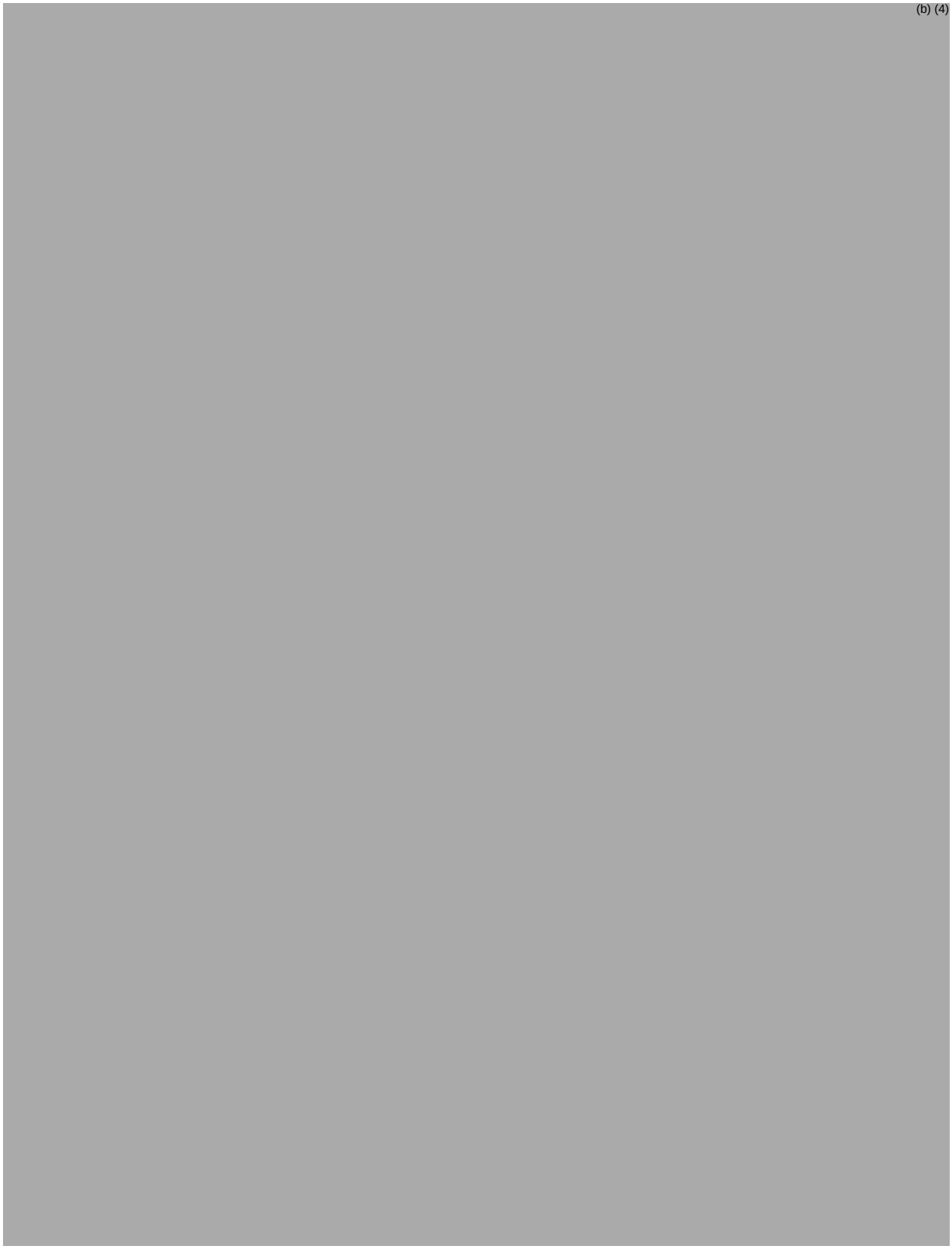
Applicant's response: As recommended by the Agency, Mylan has conducted an IVRT study, (b) (4) were estimated over the full duration of 240 minutes, (b) (4)

and results from the study demonstrate comparability for the formulation that was tested and the reference product.

(b) (4) to provide information about the mass balance. The following table summarizes information on the lots used in the IVRT study.

	Batch #	Mfg. Date	Expiry Date
Mylan's Cyclosporine Ophthalmic Emulsion	01417E	Jan. 2018	Dec. 2019
Restasis® of Allergan Inc.	96293	-	July 2019

(b) (4)


(b) (4)

Overall, based on the results of experiment mentioned above and data submitted in the Information Request Response submitted on September 26, 2017 (Sequence No. 0030), it can be reasonably concluded that the proposed IVRT method is measuring Cyclosporine released from the formulation over the complete duration of IVRT, and is not a measure of the formulation solubility in release medium. Copies of the method validation report for the measure of (b) (4) are enclosed in Section 3.2.P.5.3.

Assessor's Comments:

(b) (4)

- Per the previous BE assessment[12], the globule size was similar between the test and RLD products in the emulsion layer at all time-points over the duration of the IVRT study, demonstrating that the proposed IVRT method is measuring Cyclosporine release from the formulation and is not a measure of formulation solubility in the release media. Consequently, globule size could not be measured (b) (4) from the test and RLD products. In summary, based on the data submitted by the applicant,

[12] GDRP ANDA 205894-Orig-1-Amend-31, ORS Consult Response Review, Krishna Chimalakonda, 9/20/2017
http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

the proposed IVRT method is measuring Cyclosporine release from the formulation and is not a measure of formulation solubility in the release media.

- While the applicant submitted data requested in the CR, as the formulation of the proposed test product is not Q2 the same as the RLD, the overall BE portion of the application is **inadequate**.

4.1 Review of Applicant's Response to Bioequivalence Information Request (IR was communicated on June 28th, 2019)

IR Language:
We have potential concerns about the qualitative and quantitative (Q1/Q2) sameness of your product to the reference listed drug (RLD) with respect to inactive ingredients. Please provide an updated Components and Composition table for your test product listing the specific amount of each inactive ingredient added, (b) (4) (b) (4). Please have the updated Components and Composition table reflect the actual amounts added to the exhibit batches used in the most recent studies (i.e., batch #s 01813A, 01813B, and 03912A) that you have submitted under the in vitro bioequivalence option. If the proposed amount of any ingredient in your formulation has a range, then it is recommended that you provide the proposed mean amount as well as upper and lower limits. It is recommended that you provide the requested information in %w/w. In addition to the updated Components and Composition table, please provide information to indicate how you calculated the specific amounts of each inactive ingredient added to your formulation, as well as supporting information to include, but need not be limited to, making reference to specific lines of the relevant executed batch records.

Applicant's Response: We wish to clarify that the composition submitted in Mylan's ANDA is the same as that confirmed to be Q1/Q2 acceptable (Composition #1, Controlled correspondence Reference # 11-083, Sequence 0000, Section 1.12.15) by the Agency through a pre-submission-controlled correspondence. Mylan acknowledges that our controlled correspondence (b) (4) while all other ingredients were quantitatively specified.

While the ANDA composition table had stated (b) (4) consistent with the controlled correspondence, in practice, Mylan uses (b) (4) (b) (4) during batch manufacturing (b) (4) The revised composition provides expression in mg/mL, % w/v and % w/w terms. We wish to confirm that the unit composition and the actual amounts added to the exhibit batches used in the most recent studies (i. e. batch #s 01813A, 01813B, and 03912A) are

in alignment. We are also including dispensing sheets for batch #s 01813A, 01813B and 03912A in Section 3.2.R of this submission. (b) (4) A copy of relevant page from intended batch manufacturing record is enclosed in Section 3.2.P.3.3 of this submission.

Component	mg/mL	Theoretical Quantity/50 L	Quantity Dispensed (b) (4)
(b) (4)			(b) (4)
Cyclosporine *	(b) (4)		
Castor Oil			
Polysorbate 80			
(b) (4) anhydrous (Glycerin)			
(b) (4)			
(b) (4) (Carbomer Co-polymer Type A)			
(b) (4)			
(b) (4) sodium hydroxide (b) (4)			
Water for Injection			
(b) (4)			

Assessor's Comment: As requested in the IR, the applicant submitted updated components and composition table to reflect the actual amounts of each excipient added to the exhibit batches of the proposed test product. As seen in the table below, the amount of each excipient in the updated formulation table is very similar when compared to the formulation table submitted in the original submission[8]. (b) (4) .

Comparison of the Test product from the original submission, updated composition table and Reference Formulations				
Ingredient	**Test Product from Original submission**	**Test Product from updated Table**	**RLD[13]**	**% Difference [(T-R) / R*100%]**
	%w/w		**%w/w (mg/g)**	
Cyclosporine, USP	0.05	0.05	0.05	--
Castor Oil, USP				
Polysorbate 80, NF				
Glycerin, USP				
Carbomer Copolymer type A				
Sodium Hydroxide				
Water for injection*				

(b) (4)

(b) (4)

[13] DARRTS: NDA 50790, New/Annual Report, 1/29/2016 (Module 1.13.5, p. 7). There has been no changes to the RLD composition since its approval on 12/23/2002

- The applicant previously requested confirmation of qualitative (Q1) and quantitative (Q2) sameness in the controlled correspondence (CC #11-0183)[14]. At the time of the control, the above test formulation was considered Q1 and Q2 the same as the RLD (b) (4) (b) (4). Upon further review of the amount of these inactive ingredients in the RLD, the Agency requested the above-referenced information from the applicant. The applicant provided (b) (4) (b) (4) used in the executive batch (in the 3 exhibit batches), as in the table above, and the amount was compared to that of the RLD. Based on the information provided in the above table, the formulation of the proposed test product is Q1 the same, but not Q2 the same with respect to (b) (4) when compared to the RLD. The formulation of the proposed test product is **inadequate.**

- As the proposed test product is not Q2 the same as the RLD, it does not comply with the requirements of 314.94(a)(9)(iv). In addition, the test product does not meet the current recommendations in the draft Cyclosporine ophthalmic emulsion PSG to qualify for the in vitro BE option and does not provide adequate justification for a different approach from this recommendation. The final determination of formulation acceptability is made by OGD.

- Mylan tightened the pH range in the release specification from (b) (4) (b) (4) (b) (4). The actual pH values from three exhibit lots of the test product are (b) (4) which are comparable to the pH values (b) (4) from three exhibit lots of the RLD product[8, 15]. The acceptability of the final pH specifications is deferred to OPQ.

- Per the current Draft Guidance on Cyclosporine Ophthalmic Emulsion, the applicant should also provide comparative physicochemical characterization including the parameters such as pH, osmolality, viscosity profile as a function of applied shear, surface tension, and zeta

[14] Agency response to Control # 11-0183.
\\fda.gov\wodc\CDER\OGD\All\OGDS6\Controls\2011-docs\11-0183.pdf

potential. Applicants are also asked to submit information on drug distribution in different phases. The physicochemical properties data on the RLD and test product are provided below for *information purposes only.* The abovementioned physicochemical property data are reviewed by OPQ. Based on the OPQ reviewer's assessment, the results of drug distribution in different phases are inadequate to support the in vitro approach for bioequivalence.[15] The bioequivalence determination of cyclosporine ophthalmic emulsion, using an in vitro bioequivalence approach, is based on the totality of evidence including the assessments in the current review as well as the physicochemical data evaluated by OPQ. The bioequivalence determination will be made upon completion of the both OB and OPQ review, however as stated above the product is not eligible for the in vitro bioequivalence approach, thus no bioequivalence determination with consideration of these physicochemical data is made in this review.

- To qualify for the in vitro BE option, the applicant will be requested to reformulate the test product to be Q1/Q2 the same as the RLD product and submit in vitro data to support demonstration of bioequivalence, along with complete CMC information of the re-formulated test product for further evaluation. The applicant will be told that if it believes that the in vitro data that was already submitted is relevant to a demonstration of bioequivalence of the reformulated test product, the applicant should please provide a justification, including how the applicant proposes to bridge the prior data to the reformulated test product.

- Of note, based on previous BE assessment and ORS consult response, the methods used for IVRT and GSD studies were deemed adequate as the scientific acceptability of the

[15] GDRP ANDA-205894-Orig-1-AMEND-39. Drug Product Quality Review, Asif Rasheed, 06/17/2020 https://panorama fda.gov/project/view?ID=5b3b1c00000e159503d9fc44dd46bbb3

methodologies are formulation independent [12, 16, 17]. Further evaluation of these studies will be determined after Mylan submits its response to the identified deficiency.

4.2 Attachments

Executed batch records for batch #03912A	Executed batch Record 1.pdf
Executed batch records for batch #01813A	Executed batch Record 2.pdf
Executed batch records for batch #01813B	Executed batch Record 3.pdf

[16] GDRP ANDA 205894-Orig-1-Amend-31, ORS/DTP consult response, Darby Kozak, 09/18/17
http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882
[17] GDRP ANDA 205894-Orig-1-Amend-31, ORS/DQMM consult response, Meng Hu, 08/18/17
http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA	205894
APPLICANT	Mylan Pharmaceuticals
DRUG PRODUCT	Cyclosporine Ophthalmic Emulsion, 0.05%

The Division of Bioequivalence III (DBIII) has completed its review and has identified the following deficiency:

Based on the information currently available to the Agency and your response to the information request (IR) communicated on June 28, 2019, the formulation of your proposed test product, Cyclosporine Ophthalmic Emulsion, 0.05% is not quantitatively (Q2) the same when compared to the reference listed drug (RLD) with respect to one or more inactive ingredients. If you choose to reformulate your test product to be Q1/Q2 the same as the RLD product, you should submit in vitro data using your reformulated test product to support demonstration of bioequivalence, along with complete chemistry, manufacturing and control information for evaluation. If you believe that the in vitro data that you already submitted is relevant to a demonstration of bioequivalence of your reformulated test product, please provide a justification, including how you propose to bridge your prior data to your reformulated test product. This deficiency supersedes any prior communications regarding the acceptability of the formulation of your proposed test product, including our previous response of August 24th, 2011 to your controlled correspondence (No. 11-0183) submitted on March 4th, 2011, (and subsequent amendments on May 9th, 2011 and Aug. 4th, 2011) in which you provided formulation data, and our December 8, 2016 complete response letter.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
(Acting) Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 Outcome Page

ANDA: 205894
Completed Assignment for 205894 ID: 40436

Reviewer:	Chimalakonda, Krishna	**Date Completed:**	
Verifier:		**Date Verified:**	
Division:	Division of Bioequivalence		
Description:			

Items:

D	***Letter Date***	***Productivity Category***	***Sub Category***	***Sc re***	***Subt al***
40436	11/5/2019	BIO	ANDA Amendment [1]	1	1
4 36	1 5/201	Complexity	First Generic Drug Product Review [1]		1
4 36	1 5/201	Parallel	Minor Amendment (Original or Supplement) [1]		1
				Total	3

DIVISION OF BIOEQUIVALENCE INFORMATION REQUEST REVIEW

ANDA No.	205894		
Drug Product Name	Cyclosporine Ophthalmic Emulsion		
Strength(s)	0.05%		
Applicant Name	Mylan Pharmaceuticals		
Applicant Address	781 Chestnut Ridge Road, Morgantown, WV 26504		
US Contact Name and US Mailing Address	Anil Sachdeva 781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504		
US Contact Telephone Number	304-554-4884		
US Contact Fax Number	304-285-6407		
Original Submission Date(s)	11/01/2013		
Submission Date(s) of Amendment(s) Under Review	09/26/2017 (Response to IR)		
Primary Reviewer	Krishna Chimalakonda, Ph.D.		
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.		
Tertiary Reviewer	April C. Braddy, Ph.D.		
First Generic	Potential first generic (see section 4.1)		
Study Number(s)	CPS-CRT	CPS-CRT-00	CPS-IVR-Part IV
Study Type(s)	Comparative Physicochemical Characterization	Determination of Globule Size Distribution	Comparative In Vitro Drug Release Testing
Strength(s)	0.05%		
Analytical Site	Mylan Laboratories Clinical Research Center		
Analytical Site Address	Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent)	**Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ Not applicable		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a	☐ Possibly ☐ No ☒ N/A		

Reformulation?			
Deficiency Classification	☐ Major ☒ Minor/CR ☐ N/A		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	*Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)* ☒ Recommended/Latest Revision Date: 10/2016 RLD Number: NDA 050790 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1, 13	Formulation Q1/Q2	0.05%	☒ Adequate ☐ Inadequate
1, 13, 31	Globule Size Distribution		☒ Adequate ☐ Inadequate
1, 13, 31, 34	In vitro Release Testing		☐ Adequate ☒ Inadequate
1, 13, 31, 34	Waiver		☐ Adequate ☒ Inadequate

1 EXECUTIVE SUMMARY

This is a bioequivalence (BE) review of the firm's response to the information request (IR) dated Sep. 20, 2017[1].

Per the original BE review[2], test product formulation is Q1/Q2 the same as the RLD. To demonstrate bioequivalence, the firm submitted data on globule size distribution (GSD) using dynamic light scattering (DLS) and in vitro release testing (IVRT) using rotating bottle dissolution apparatus. In the complete response letter (CRL) communicated to the firm on Dec. 08, 2016[3], the pivotal GSD and IVRT data were inadequate and the firm was requested to submit additional information. In response to the CRL, the firm submitted all the requested data for GSD and IVRT method validation and conducted statistical analysis to demonstrate equivalence based on the shape of the GSD profile between the test and RLD products. Based on the consult response[4] from the Division of Quantitative Methods and Modeling (DQMM), the GSD data demonstrated that test product is equivalent to the RLD based on the shape of the GSD profiles and the pivotal GSD study is adequate[5].

Based on consult response[6] from the Division of Therapeutic Performance (DTP), the pivotal IVRT study was inadequate[5] and an IR was sent to request additional information to demonstrate that the proposed IVRT method is measuring cyclosporine released from the formulation and is not a measure of formulation solubility in the release media. Specifically, the firm was requested to submit data on the mass balance of key formulation components (b) (4) (b) (4) and measurement of globule size (b) (4) (b) (4) over the complete duration of the IVRT study.

In the current submission, the firm submitted data on the mass balance of cyclosporine and determined globule size (b) (4). The firm did not submit data on the mass balance of (b) (4). The firm will be requested to

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[1] GDRP ANDA 205894-Orig-1-Amend-31, Pariban Dhanormchitphong, 9/20/2017. last accessed date: 12/7/17
http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

[2] GDRP ANDA 205894-Orig-1, Bioequivalence Primary Review, Krishna Chimalakonda, 11/02/2016. Last accessed on 12/7/17
http://panorama.fda.gov/task/view?ID=542124870034e8954709b1d5fdbbfa41

[3] GDRP ANDA 205894-Orig-1, ANDA action-09, Complete response, 12/8/2016
http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

[4] GDRP ANDA 205894-Orig-1-Amend-31, ORS/DQMM consult response, Meng Hu, 08/18/17. Last accessed date on 12/7/17
http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

[5] GDRP ANDA 205894-Orig-1-Amend-31, ORS Consult Response Review, Ke Ren, 9/20/2017. last accessed date: 12/7/17
http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

[6] GDRP ANDA 205894-Orig-1-Amend-31, ORS/DTP consult response, Darby Kozak, 09/18/17. Last accessed date on 12/7/17
http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

submit this information. The firm's response is inadequate and pivotal IVRT study is inadequate.

OSIS Status "Complete"

Office of Scientific Integrity and Surveillance (OSIS) conducted a routine inspection of the analytical portion for the GSD and IVRT studies. No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI)[7]. OSIS concludes the data from the audited studies are reliable and recommends the analytical data from studies CPS-IVR Part-IV and CPS-CRT Part-II and other studies using similar methods be accepted for further Agency review. In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status of the current ANDA is complete.

The Division of Bioequivalence III (DBIII) does not grant the waiver request due to deficiency related to the IVRT study. The BE portion of the application is **inadequate**.

[7] GDRP ANDA 205894-Orig-1-Amend-31, Nicola Fenty-Stewart, 4/06/2018. last accessed date: 4/12/17

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3 SUBMISSION SUMMARY

3.1 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	Yes	1
In Vitro Release Testing	Yes	1
Globule Size Distribution	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

3.2 Waiver Request(s)

Strengths for which waivers are requested, if applicable	0.05%
Waiver regulation cited?	21 CFR § 320.24 (b) (6)
Strengths considered for 21 CFR 320.24 (b)(6)	0.05%
Proportional to strength tested in vivo?	N/A
Is IVRT study acceptable?	No
Waivers granted?	**No**
If not then why?	Due to deficiency related to IVRT study.

3.3 Deficiency Comments

See deficiency letter.

3.4 Recommendations

The Division of Bioequivalence III (DBIII) does not agree that the information submitted by Mylan Pharmaceuticals, demonstrates that its test product, Cyclosporine Ophthalmic Emulsion, 0.05%, meets the requirements of Section 21 CFR § 320.24 (b) (6), along with the current DB recommendations for ophthalmic drug products, due to the deficiencies specified in the letter. The DBIII denies the waiver of bioequivalence testing.

3.5 Comments for Other OGD Disciplines

Discipline	Comment

None

3.6 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
None	

4 INFORMATION REQUEST RESPONSE REVIEW

Deficiency Related To In Vitro Release Testing (IVRT)

Deficiency 1: *Your in vitro drug release testing (IVRT) study (No. CPS-IVR-Part IV) using the rotating bottle dissolution apparatus is inadequate. Please provide sufficient data and/or justification to demonstrate that your proposed IVRT method is measuring cyclosporine released from the formulation over the complete duration of the IVRT and is not a measure of the formulation solubility in the release media. This can include, but is not limited to, the information on mass balance of key formulation components* (b) (4) *and characterization of physicochemical properties (e.g. measurement of globule size* (b) (4) *over the complete duration of the IVRT.*

Firm's response: As requested by the Agency, Mylan has conducted In Vitro Release Test (IVRT) to demonstrate the proposed IVRT method is suitable for measuring the drug release from the emulsion. The IVRT was conducted in both the test and reference product over a period of 240 minutes per the established experimental conditions. The samples withdrawn over a period were tested for both Cyclosporine content and globule size. There was a gradual release of Cyclosporine from the emulsion in both the test and reference products. There was no significant change in the mean globule size observed over the period of release testing in both the test and reference product. The results confirm that the proposed IVRT method can release the drug (Cyclosporine) (b) (4) (b) (4) and is not a measure of formulation solubility in the release media. The details of the study conducted are provided below. (b) (4) . The composition of Mylan's Cyclosporine Ophthalmic Emulsion and function of each ingredient are given below in Table 1.

Table 1: Composition of Cyclosporine Ophthalmic Emulsion

Ingredient	Grade	Function	% w/v	Qty (mg/mL)
Cyclosporine	USP	Active	0.05	(b) (4)
Castor Oil (b) (4)	USP	(b) (4)		
Polysorbate 80 (b) (4) (b) (4)	USP-NF			
Glycerin	USP			
Carbomer Co-Polymer Type-A (b) (4)	USP-NF			
Sodium Hydroxide	USP-NF	pH adjusting agent	(b) (4) adjust pH (6.5 – 8.0)	(b) (4) adjust pH
Water for Injection	USP	(b) (4)		

(b) (4)

The emulsion components can distribute themselves in various phases depending on their physicochemical properties as well as the process of manufacture of the emulsion. The drug distribution in various phases and the drug release from the emulsion into the various ocular tissues are explained in Annexure 1 enclosed in Section 1.12.15 of this submission.

To demonstrate that the proposed IVRT method is measuring Cyclosporine released from the formulation over the complete duration of the IVRT and is not a measure of the formulation solubility in the release media, both the test and the reference samples were subjected to the in vitro release testing. (b) (4)

(b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

Based on collective interpretation that can be drawn from all the above experimental and data based facts, it is evident that the current IVRT method is a reflection of cyclosporine release from the formulation over the complete duration of the IVRT and is not a measure of the formulation solubility in the release media.

Reviewer's comment:

In summary, the firm was previously requested to (1) measure mass balance of cyclosporine, (b) (4) and (2) measure globule size (b) (4) over the complete duration of the IVRT study. In their response, the firm measured only the mass balance of cyclosporine and determined globule size (b) (4). The firm did NOT measure mass balance (b) (4) The firm will be requested to submit this information. The firm's response is inadequate and pivotal IVRT study is inadequate.

4.1 Attachments

Consult response from DTP	DTP Consult Response for A20589
Consult response from DQMM	ANDA205894_Mylan_ Consult_response.doc
OGD/ORS/OPQ Meeting slides from Dec 18th, 2017	Dec 2017 update on cyclosporine emu
Firm's response to IR	Firms Response to IR.pdf

[8] DTP consult response slides for IVRT ANDA 205894, Darby Kozak, 09/13/17 http://panorama.fda.gov/project/view?ID=589d61f10099fd01db32c013ed18a882

Email from RPM: This is a potential first generic. There is a filing issue where all the cyclosporine ANDAs were RTR and then rescinded and this falls in that. Policy is currently trying to sort out which would qualify as first filers, if any. This is a pretty complicated situation.

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 205894

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Cyclosporine Ophthalmic Emulsion, 0.05%

The Division of Bioequivalence III (DBIII) has completed its review of your response to the information request (IR) dated Sept. 20, 2017 and has identified the following deficiency (*to be communicated as complete response*):

Your in vitro drug release testing (IVRT) study (No. CPS-IVR-Part IV) using the rotating bottle dissolution apparatus is inadequate. As requested previously in the IR dated Sept. 20, 2017, please provide information on mass balance of [redacted] (b) (4) [redacted] (b) (4) from your proposed test product and the reference listed drug (RLD) product; Restasis®, over the complete duration of the IVRT study.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 Outcome Page

ANDA 205894
Completed Assignment for 205894 ID: 34674

Reviewer: Chimalakonda, Krishna **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description:
Items:

ID	Letter Date	Productivity Category	Sub Category	Score	Subtotal		
34674	9/26/2017	BIO	IR Response Review [1]	1	1	Edit	Delete
34674	9/26/2017	Complexity	First Generic Drug Product Review [1]	1	1	Edit	Delete
34674	9/26/2017	Complexity	In vitro Release Test (IVRT) [0.5]	1	1	Edit	Delete
34674	9/26/2017	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1	Edit	Delete
				Total:	**4**		

Division of Bioequivalence Complete Response Review

ANDA No.	205894
Drug Product Name	Cyclosporine Ophthalmic Emulsion
Strength(s)	0.05%
Applicant Name	Mylan Pharmaceuticals
Applicant Address	781 Chestnut Ridge Road, Morgantown, WV 26505
Applicant's Point of Contact	Joseph J. Sobecki, 781 Chestnut Ridge Road, Morgantown, WV 26505
Contact's Telephone Number	304-599-2595
Contact's Fax Number	304-285-6407
Contact's Email	Joseph. Sobecki@mylan.com
Original Submission Date(s)	11/01/2013
Submission Date(s) of Amendment(s) Under Review	02/08/2017 (Response to CR)
First Generic	Potential first generic (see section 4.3)
Primary Reviewer	Krishna Chimalakonda, Ph.D.
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.
Tertiary Reviewer	April C. Braddy, Ph.D.
Study Number (s)	CPS-CRT
Study Type (s)	Comparative Physicochemical Characterization
Strength (s)	0.05%
Analytical Site	Mylan Laboratories Clinical Research Center, Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India
Study Number (s)	CPS-CRT-00
Study Type (s)	Determination of Globule Size Distribution
Strength (s)	0.05%
Analytical Site	Mylan Laboratories Clinical Research Center, Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India
Study Number (s)	CPS-IVR-00
Study Type (s)	Comparative In Vitro Drug Release Testing
Strength (s)	0.05%
Analytical Site	Mylan Laboratories Clinical Research Center, Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☒ Pending ☐ Complete **Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete
Biowaiver	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ Not applicable

QC IVRT study	☒ Pending ☐ Adequate ☐ Inadequate ☐ Not applicable		
Formulation	☒ Adequate ☐ Inadequate		
Overall Review Result	☐ Adequate ☒ Inadequate		
Revised/new Draft Guidance Included	☐ YES ☒ NO		
Communication	☒ ECD ☐ IR ☐ Not Applicable		
Deficiency Classification	☐ Major (Deficiencies to be communicated by CR) ☒ Minor ☐ N/A (Review is Adequate)		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 13	**Formulation Q1/Q2**	**0.05%**	**Adequate**
1, 13, 31	**Globule Size Distribution**	**0.05%**	**Inadequate**
1, 13, 31	**In vitro Release Testing**	**0.05%**	**Adequate**
1, 13, 31	**Waiver**	**0.05%**	**Inadequate**

1 EXECUTIVE SUMMARY

This is a bioequivalence (BE) review of the firm's response to the Agency's complete response (CR) letter dated December 08, 2016[1].

Per the original BE review[2], test product formulation is Q1/Q2 the same as the RLD. To demonstrate bioequivalence, the firm submitted data on the comparative globule size distribution (GSD) using dynamic light scattering (DLS) and in vitro release testing (IVRT) using rotating bottle dissolution apparatus. Based on the consult response[3] on the data submitted in the original submission, the pivotal GSD and IVRT studies were inadequate and the firm was requested to address the following deficiencies, in addition to providing information as outlined in the revised drug product specific guidance document[4].

- Repeat GSD method validation using RLD samples.
- Clarify which GSD data are from the test and reference samples.
- Based on the revised draft guidance[4], additional data should be submitted to demonstrate equivalence between the test and RLD formulations in the shape of the globule size distribution (such as the presence of multiple peaks). See section 4.3 for consult response from the Office of Research Standards (ORS).
- Submit comparative GSD data and size distribution profiles (histograms) for both undiluted samples and upon dilution of the test product and RLD.
- Submit pre-study method development and validation report for the IVRT study.

In the current submission, the firm submitted all the requested data for the IVRT study using a validated rotating bottle dissolution apparatus method. The firm's response is adequate and pivotal IVRT study is adequate. For the pivotal GSD study, the firm did not submit SAS transport files to assess the difference (in terms of distance) between the shapes of globule size distribution profiles of the test product and RLD. The firm will be requested to submit this information. The firm's response is inadequate. The pivotal GSD study is inadequate.

There are multiple Office of Scientific Integrity and Surveillance (OSIS) inspections for the analytical site used in the current application. However, all the inspected studies pertain to inspection of the analytical portion of fasting and fed BE studies. There is no inspection history for the analytical site which is related to GSD and IVRT studies. A

[1] GDRP ANDA 205894-Orig-1, David Foss, 12/08/2016. last accessed date: 04/25/17
http://panorama.fda.gov/project/view?ID=542124860034e6989063c64da15eca8c
[2] GDRP ANDA 205894-Orig-1, Bioequivalence Primary Review, Krishna Chimalakonda, 11/02/2016. Last accessed on 04/25/2017
http://panorama.fda.gov/task/view?ID=542124870034e8954709b1d5fdbbfa41
[3] GDRP ANDA 205894-Orig-1, ORS/DTP consult response, Mohammad Absar, 08/11/16. Last accessed date: 06/05/2017
http://panorama.fda.gov/task/view?ID=542124870034e8954709b1d5fdbbfa41
[4] Draft Guidance on Cyclosporine: Last accessed on 04/25/2017
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf

routine inspection of the analytical portion of the GSD and IVRT studies will be requested for the current application. Therefore, the overall OSIS inspection status for the current ANDA is considered pending at this time.

The Division of Bioequivalence III (DB III) does not grant the waiver request due to deficiency related to GSD study and pending OSIS inspection of the analytical site.

The application is **inadequate** with deficiencies.

Please refer to the consult response review[5] for the deficiency related to the IVRT study and the final outcome on the GSD and IVRT studies.

[5] GDRP ANDA 205894-Orig-1-Amend-31, Consult response review, Krishna Chimalakonda, 09/20/2017. Last accessed on 09/20/2017

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	Yes	1
In Vitro Release Testing	Yes	1
Globule Size Distribution	Yes	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

3.2 Waiver Request(s)

Strengths for which waivers are requested, if applicable	0.05%
Waiver regulation cited?	21 CFR § 320.24 (b) (6)
Strengths considered for 21 CFR 320.24 (b)(6)	0.05%
Proportional to strength tested in vivo?	N/A
Is IVRT study acceptable?	Yes
Waivers granted?	**No**
If not then why?	Due to minor deficiency related to GSD study and pending OSIS inspection of the analytical site.

3.3 Deficiency Comments

See deficiency letter.

3.4 Recommendations

The Division of Bioequivalence III (DBIII) does not agree that the information submitted by Mylan Pharmaceuticals, demonstrates that its test product, Cyclosporine Ophthalmic Emulsion, 0.05%, meets the requirements of Section 21 CFR § 320.24 (b) (6), along with the current DB recommendations for ophthalmic drug products, due to the deficiencies specified in the letter. The DBIII denies the waiver of bioequivalence testing.

3.5 Comments for Other OGD Disciplines

Discipline	Comment

Office of Pharmaceutical Quality (OPQ)	Please note the acceptability of this application is deferred to OPQ for reviewing the physicochemical properties.

3.6 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
None	

APPEARS THIS WAY ON ORIGINAL

4 AMENDMENT REVIEW

Deficiencies Related To Globule Size Distribution Testing

Deficiency 1: *Your pivotal GSD study is inadequate due to deficiencies outlined below. Please submit additional GSD data based on the revised draft guidance on Cyclosporine ophthalmic emulsion, 0.05% (October 2016) for Agency's recommendation on comparative GSD testing.*

Firm's response: Mylan acknowledges Agency's comment. The responses pertaining to the comments raised by the Agency based on the revised draft guidance dated October 2016 is provided below.

Reviewer's comment:
Please refer to reviewer's comments below for firm's response to deficiencies.

Deficiency 2: *Based on the revised draft guidance, additional data should be submitted to demonstrate equivalence between the test and RLD formulations in the shape of the globule size distribution (such as the presence of multiple peaks). Considering the multi-modal nature of cyclosporine globule size distribution, please use a high resolution method (such as narrow mode) that is capable of separating individual peaks.*

Firm's response: As recommended by the Agency, the globule size distribution data which was generated as part of the globule size distribution study using general purpose mode has been reprocessed to generate this additional data using high resolution method i. e. narrow mode. The method used to reprocess the data is provided in study protocol # SP-CPS-CRT, part-II, Supplement-01, version-00. This protocol is part of the study report # CPS-CRT Part-II, Supplement-01, version-00, enclosed in Section 1.12.15. Please note that the results of the study i.e. comparative globule size distribution (Z-average and PdI) using narrow mode and other important information such as bin size/number, number of channels, acquisition time (seconds) and mean count rate (kcps) are summarized in the enclosed report. Also, the histogram of each sample is provided as attachment-2B.

Reviewer's comment:
In the current submission, the firm submitted comparative GSD data using a high resolution method, i. e. narrow mode, on 3 lots of the test product (Nos. 01813A, 01813B, 03912A) and RLD (Nos. 80773, 80776, 81028) using undiluted and serially diluted samples (25-, 50-, 100-, and 200-fold). The firm did not submit SAS transport files to assess the difference (in terms of distance) between the shapes of globule size distribution profiles of the test product and RLD. Therefore, statistical analysis to demonstrate equivalence between the test and RLD formulations cannot be determined at this time. The firm will be requested to submit this data. Firm's response is inadequate. The pivotal GSD study is inadequate.

Deficiency 3: *Your GSD method validation is inadequate as validation data was generated using the test product. Please repeat GSD method validation using only the RLD samples. Accuracy determination should be evaluated using reference standard particles.*

Firm's response: As recommended by the Agency, the globule size distribution method validation is performed using RLD samples. Also, as recommended, accuracy studies have been performed using reference standard particles. Testing for remaining parameters has been performed using RLD (Restasis®) samples.

The details of the reference standard particles and RLD samples used during validation study are summarized in the table below. A copy of the analytical method validation report for the determination of GSD of cyclosporine ophthalmic emulsion, report # VR-134; supplement-02, version-00 is enclosed in Section 1.12.15.

(b) (4)

Reviewer's comment:

The firm submitted GSD method validation data using the RLD (batch # 90892) and submitted method accuracy data using NIST traceable standards (60 nm and 200 nm). The firm validated the GSD method for system and method precision, intermediate precision, robustness (by varying chamber temperature, equilibration time, number of measurements, and sample dilution) and stability of the emulsion. GSD method validation is adequate. Firm's response is adequate.

Accuracy

Accuracy of the GSD method was evaluated using NIST traceable standards. Per the table below, individual Z-average value for 18 measurements per standard (60 and 200 nm) were within the range of (b) (4), respectively, with very low variability (% RSD ranges from (b) (4). The accuracy data for Z-average and poly-dispersity index (PDI) meets the pre-defined acceptance criteria (see table below). The accuracy data is acceptable.

Table 1: Accuracy

File Name: Accuracy-040117

Record	Sample Name	Z-Ave (d.nm)	PDI	Record	Sample Name	Z-Ave (d.nm)	PDI	Record	Sample Name	Z-Ave (d.nm)	PDI
1	Accuracy-60nm-040117-01		(b) (4)	7	Accuracy-60nm-040117-02		(b) (4)	13	Accuracy-60nm-040117-03		(b) (4)
2	Accuracy-60nm-040117-01			8	Accuracy-60nm-040117-02			14	Accuracy-60nm-040117-03		
3	Accuracy-60nm-040117-01			9	Accuracy-60nm-040117-02			15	Accuracy-60nm-040117-03		
4	Accuracy-60nm-040117-01			10	Accuracy-60nm-040117-02			16	Accuracy-60nm-040117-03		
5	Accuracy-60nm-040117-01			11	Accuracy-60nm-040117-02			17	Accuracy-60nm-040117-03		
6	Accuracy-60nm-040117-01			12	Accuracy-60nm-040117-02			18	Accuracy-60nm-040117-03		
	Average				**Average**				**Average**		
	STD				**STD**				**STD**		
	%RSD				**%RSD**				**%RSD**		
	Certified Mean Diameter				**Certified Mean Diameter**				**Certified Mean Diameter**		
	% Nominal				**% Nominal**				**% Nominal**		
Record	**Sample Name**	**Z-Ave (d.nm)**	**PDI**	**Record**	**Sample Name**	**Z-Ave (d.nm)**	**PDI**	**Record**	**Sample Name**	**Z-Ave (d.nm)**	**PDI**
19	Accuracy-200nm-040117-01		(b) (4)	25	Accuracy-200nm-040117-02		(b) (4)	31	Accuracy-200nm-040117-03		(b) (4)
20	Accuracy-200nm-040117-01			26	Accuracy-200nm-040117-02			32	Accuracy-200nm-040117-03		
21	Accuracy-200nm-040117-01			27	Accuracy-200nm-040117-02			33	Accuracy-200nm-040117-03		
22	Accuracy-200nm-040117-01			28	Accuracy-200nm-040117-02			34	Accuracy-200nm-040117-03		
23	Accuracy-200nm-040117-01			29	Accuracy-200nm-040117-02			35	Accuracy-200nm-040117-03		
24	Accuracy-200nm-040117-01			30	Accuracy-200nm-040117-02			36	Accuracy-200nm-040117-03		
	Average				**Average**				**Average**		
	STD				**STD**				**STD**		
	%RSD				**%RSD**				**%RSD**		
	Certified Mean Diameter				**Certified Mean Diameter**				**Certified Mean Diameter**		
	% Nominal				**% Nominal**				**% Nominal**		

(b) (4)

System Precision

The precision of the test system was evaluated by six replicate measurements of a homogenous sample solution at 100 times dilution of the RLD. Per the table below, the precision data for Z-average and PDI meets the pre-defined acceptance criteria, with low variability. The system precision data is acceptable.

Table 2: System Precision

File Name: System precision 050117

Sr. No.	Sample Name	Z-Average	PDI
1	System Precision_050117 1		(b) (4)
2	System Precision_050117 2		
3	System Precision_050117 3		
4	System Precision_050117 4		
5	System Precision_050117 5		
6	System Precision_050117 6		
N			
Average			
SD			
% RSD			

(b) (4)

Method Precision

Method precision was evaluated from multiple sampling of same homogeneous RLD at 100 times dilution by taking the average of each measurement of six different homogenous samples. Per the table below, the precision data for Z-average and PDI meets the pre-defined acceptance criteria, with low variability. The system precision data is acceptable.

Table 3: Method Precision

File Name: Method precision 050117

Sr. No.	Sample Name	Z-Average	PDI
1	Method Precision_050117-1 1		(b) (4)
2	Method Precision_050117-2 1		
3	Method Precision_050117-3 1		
4	Method Precision_050117-4 1		
5	Method Precision_050117-5 1		
6	Method Precision_050117-6 1		
N			
Average			
SD			
% RSD			

(b) (4)

Intermediate Precision (different day and different analyst)

The intermediate precision of the method on different day by different analyst was evaluated by taking the average of single measurement of six different homogenous samples. Per the table below, the intermediate precision data for Z-average and PDI meets the pre-defined acceptance criteria, with low variability. The intermediate precision data is acceptable.

Table 4: Intermediate Precision

File Name: Intermediate precision-Rep-060117

Sr. No.	Sample Name	Z-Average	PDI
1	Intermediate precision-Rep-060117-1 1		(b) (4)
2	Intermediate precision-Rep-060117-2 1		
3	Intermediate precision-Rep-060117-3 1		
4	Intermediate precision-Rep-060117-4 1		
5	Intermediate precision-Rep-060117-5 1		
6	Intermediate precision-Rep-060117-6 1		
N			
Average			
SD			
% RSD			

(b) (4)

Robustness

Varying chamber temperature

The analysis was performed by varying the chamber temperature by ± 2°C from set temperature of 25°C i.e. at 23°C & 27°C. One sample for three measurements at 100 times dilution were analyzed at each temperature. Per the table below, the robustness data for Z-average and PDI meets the pre-defined acceptance criteria, with low variability. The robustness data is acceptable.

Table 5: Robustness by varying chamber temperature

File Name: Robustness-Temperature-050117

Sample Name	Z-Ave(d.nm)	PDI
Temperature 25°C		
Robustness-25°C 1		(b) (4)
Robustness-25°C 2		
Robustness-25°C 3		
Average		
Std Dev.		
% RSD		
Temperature 23°C		
Robustness-23°C 1		(b) (4)
Robustness-23°C 2		
Robustness-23°C 3		
Average		
Std Dev.		
% RSD		
% Variation		
Temperature 27°C		
Robustness-27°C 1		(b) (4)
Robustness-27°C 2		
Robustness-27°C 3		
Average		
Std Dev.		
% RSD		
% Variation		

(b) (4)

Varying equilibration time

The analysis was performed by varying the equilibration time by ± 10 sec from set time of 120 sec i.e. at 110 sec & 130 sec. One sample for three measurements at 100 times dilution at each condition was analyzed. Per the table below, the robustness data for Z-average and PDI meets the pre-defined acceptance criteria, with low variability. The robustness data is acceptable.

Table 6: Robustness by varying equilibration time

File Name: Robustness-Equilibration-050117

Sample Name	Z-Ave(d.nm)	PDI
Equilibration-120 Sec		
Robustness-Equilibration-120 sec 1		(b) (4)
Robustness-Equilibration-120 sec 2		
Robustness-Equilibration-120 sec 3		
Average		
Std Dev.		
% RSD		
Equilibration-110 Sec		
Robustness-Equilibration-110 sec 1		(b) (4)
Robustness-Equilibration-110 sec 2		
Robustness-Equilibration-110 sec 3		
Average		
Std Dev.		
% RSD		
% Variation		
Equilibration-130 Sec		
Robustness-Equilibration-130 sec 1		(b) (4)
Robustness-Equilibration-130 sec 2		
Robustness-Equilibration-130 sec 3		
Average		
Std Dev.		
% RSD		
% Variation		

(b) (4)

Varying number of measurements

The analysis was performed by varying number of measurements by ± 1 from 3 measurements i.e. at 2 & 4 measurements. One sample was analyzed at two and four measurements at 100 times dilution. Per the table below, the robustness data for Z-average and PDI meets the pre-defined acceptance criteria, with low variability. The robustness data is acceptable.

Table 7: Robustness by varying number of Measurements

File Name: Robustness-Measurements-050117

Sample Name	Z-Ave(d.nm)	PDI
Measurements 2		
Robustness-Measurements_2 1		(b) (4)
Robustness-Measurements_2 2		
Average		
Std Dev.		
% RSD		
% Variation		
Measurements 3		
Robustness-Measurements_3 1		(b) (4)
Robustness-Measurements_3 2		
Robustness-Measurements_3 3		
Average		
Std Dev.		
% RSD		
Measurements 4		
Robustness-Measurements_4 1		(b) (4)
Robustness-Measurements_4 2		
Robustness-Measurements_4 3		
Robustness-Measurements_4 4		
Average		
Std Dev.		
% RSD		
% Variation		

(b) (4)

Effect of sample dilution

The analysis was performed by varying the sample dilution ranging from no dilution to 200 times dilution i.e. undiluted, 25X, 50X, 100X & 200X. One sample was analyzed for 6 measurements at all dilutions (undiluted, 25X, 50X, 100X & 200X). Per the table below, the robustness data for Z-average and PDI meets the pre-defined acceptance criteria, with low variability. The robustness data is acceptable.

Table 8: Robustness by Effect of sample dilution

File Name: Robustness-Sample Dilution-050117

Sample Name	Z-Ave(d.nm)	PDI
Robustness-As Such sample 1		(b) (4)
Robustness-As Such sample 2		
Robustness-As Such sample 3		
Robustness-As Such sample 4		
Robustness-As Such sample 5		
Robustness-As Such sample 6		
Average		
STD		
%RSD		
Robustness-50X 1		
Robustness-50X 2		
Robustness-50X 3		
Robustness-50X 4		
Robustness-50X 5		
Robustness-50X 6		
Average		
STD		
%RSD		
% Variation		
Robustness-100X 1		
Robustness-100X 2		
Robustness-100X 3		
Robustness-100X 4		
Robustness-100X 5		
Robustness-100X 6		
Average		
STD		
%RSD		
Robustness-200X 1		
Robustness-200X 2		
Robustness-200X 3		
Robustness-200X 4		
Robustness-200X 5		
Robustness-200X 6		
Average		
STD		
%RSD		
% Variation		

Sample Name	Z-Ave(d.nm)	PDI
Robustness-25XRep 1		(b) (4)
Robustness-25XRep 2		
Robustness-25XRep 3		
Robustness-25XRep 4		
Robustness-25XRep 5		
Robustness-25XRep 6		
Average		
STD		
%RSD		
% Variation		

(b) (4)

Stability at room temperature

Three (3) aliquots of 100 times diluted cyclosporine ophthalmic emulsion were prepared and one aliquot was analyzed immediately. Two other aliquots were kept on the bench as stability samples and these samples were analyzed after 4 hrs 6 minutes [aliquot-2] and 6 hrs. 7 minutes [aliquot-3]. Per the table below, the Z-average and PDI data meet the pre-defined acceptance criteria, with low variability. The samples were found to be stable at room temperature for up to 6 hrs. 7 minutes.

Table 9: Stability at room temperature

File Name: Stability-060117

Sample Name	Z-Ave(d.nm)	PDI
Comparison (initial)		
Stability- Initial 1		(b) (4)
Stability- Initial 2		
Stability- Initial 3		
Stability- Initial 4		
Stability- Initial 5		
Stability- Initial 6		
Average		
Std Dev.		
% RSD		
Stability after 4 hr 6 min		
Stability- 4hrs 1		(b) (4)
Stability- 4hrs 2		
Stability- 4hrs 3		
Stability- 4hrs 4		
Stability- 4hrs 5		
Stability- 4hrs 6		
Average		
Std Dev.		
% RSD		
% Variation		
Stability after 6 hr 7 min		
Stability-6hrs 1		(b) (4)
Stability-6hrs 2		
Stability-6hrs 3		
Stability-6hrs 4		
Stability-6hrs 5		
Stability-6hrs 6		
Average		
Std Dev.		
% RSD		
% Variation		

(b) (4)

Deficiency 4: *You provided data from individual samples on the Z-average size, PdI, D10, D50 and SPAN. Please clarify which data are from the test and reference samples. Please also compare the shape of the intensity histogram between the test and reference products. Equivalence in shape should be demonstrated by a suitable statistical method. In this regard, please also submit the raw data for the intensity histogram for the Agency's evaluation.*

Firm's response: Mylan would like to clarify to the Agency that attachment-5: cyclosporine particle size distribution data listing which is submitted as part of attachment A: Statistical Study Report under CPS-PBE report version-00; part-III clearly defines the reference and test samples lot numbers. Regarding evaluation of shape of the intensity histogram between the test and reference products, please refer to the attachment-2B (part 1, part-2 and part-3) of study report on population bioequivalence based on Z-average and PDI [report #: CPS-PBE, version #-00, part-III, supplement-01] enclosed in section 1.12.15 of this submission. Further, as recommended by Agency, Mylan has used a statistical method (earth mover's distance method) to demonstrate the equivalency in shape of the intensity histogram of RLD and test product. The statistical summary report is enclosed as attachment-4 to CPS-PBE, report version number-00, part-III, supplement-01 in Section 1.12.15 (see summary BE table below).

Summary of GSD Results: PBE Analysis on GSD Data: Firm's Calculation

Table1

	Geometric mean		Geometric Mean Ratio	Standard Deviation		SigmaT/SigmaR Ratio
Variable	Test	Reference		SigmaT	SigmaR	
EMD						

(b) (4)

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	95% Upper CB <0? Pass or Fail PBE
Reference-scaled			Pass

(b) (4)

Reviewer's comment:

In the current submission, the firm clarified the GSD data which corresponds to test and reference samples and submitted raw data for the intensity histogram. However, the firm did not submit shape of the GSD data of the test product and RLD is SAS transport files. Therefore, statistical analysis to demonstrate equivalence between the test and RLD formulations in the shape of the GSD cannot be conducted. The firm will be requested to submit this data. Firm's response is inadequate.

Deficiency 5: *You provided comparative GSD data from 100x diluted samples. Please also provide GSD data from undiluted samples and upon serial dilution.*

Firm's response: Mylan would like to clarify to the Agency that the GSD analysis was performed on undiluted and serially diluted samples and the same was submitted to the Agency's attention through sequence the Information Request Response dated July 21, 2016 (Sequence No. 0024). Further, this data has been reprocessed using high intensity narrow mode as per the Agency's revised October 2016 BE recommendation. Please note, this reprocessed data is summarized in the report "Study Number: CPS-GSD-CRT Part-II, Supplement-01; Report Version No.:00. attachment-2B- part-1 and 2" which is enclosed in Section 1.12.15 of this submission.

Reviewer's comment:

In the current submission, the firm submitted GSD data using narrow mode on 3 lots of the test product (Nos. 01813A, 01813B, 03912A) and RLD (Nos. 80773, 80776, 81028) using undiluted and serially diluted (25-, 50-, 100-, and 200-fold) samples. The firm's response is adequate.

Deficiency 6: *Please submit the standard operating procedure (SOP; #AMP-134-00) for the GSD method that was effective during the conduct of the GSD study.*

Firm's response: Mylan would like to clarify to the Agency that the requested standard operating procedure (SOP# AMP-134-00) for GSD method was submitted in the Original ANDA submission (Sequence No. 0000) as well as in the Information Request Response dated July 10, 2015 (Sequence No. 0011) as a part of the physicochemical characterization report part-II (page 37 through 42) for the biowaiver submitted under Section 1.12.15. Further, this SOP has been revised to include high intensity narrow mode as per the Agency's revised October 2016 BE recommendation. A copy of current version of this SOP (SOP # AMP-134-01) is provided as a part of report study report number CPS-CRT Part-II, Supplement-01, version-00 enclosed in Section 1.12.15 of this submission.

Reviewer's comment:
In the current submission, the firm submitted SOP (# AMP-134-01) for the GSD method that was effective during the conduct of the GSD study. The firm's response is adequate.

Deficiency 7: *Please provide the correlation decay curve for each sample. In addition, please specify the bin size/number used during the measurement. Please also specify the count rate, acquisition time, and number of channels that was used in the DLS method. We encourage you to keep these parameters fixed throughout the experiment.*

Firm's response: As requested by the Agency, correlation decay curve for each sample is provided as part of revised globule size distribution study using narrow mode under report # CPS-CRT Part-II, Suppliment-01, Report Version No. : 00, Attachment-2C. Please note that the bin size/number and number of channels were kept constant throughout the study. The count rate and acquisition time (duration time) are sample specific for each measurement. The data for all these parameters is provided in report namely CPS-CRT Part-II, Supplement-01, Report Version No. 00, Table 1A and Attachment-2A. The analytical method procedure AMP-01 describes the instrument parameters which are kept constant.

Reviewer's comment:
In the current submission, the firm provided correlation decay curve for each sample. The correlation coefficient of the decay curve for each sample is (b) (4) As shown in the table below, the firm submitted information on bin number, number of channels, acquisition time (seconds) and count rate (kcps). Number of bins and channels were kept constant throughout the experiment. The firm's response is adequate.


(b) (4)

4.1 Pivotal Globule Size Distribution Results

Summary of GSD Results: PBE Analysis Results on GSD Data, Firm's Calculation

Table1

	Geometric mean		Geometric Mean Ratio	Standard Deviation		SigmaT/SigmaR Ratio
Variable	Test	Reference		SigmaT	SigmaR	
EMD			(b) (4)			

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	95% Upper CB <0? Pass or Fail PBE
Reference-scaled	(b) (4)		Pass

Reviewer's Comments

1. The firm conducted GSD study on 10 samples/lot using three lots each of the test product (Nos. 01813A, 01813B, and 03912A) and the RLD (Nos. 80773, 80796 & 81028). In agreement with the ORS consult response[3] and the draft product specific guidance[4], samples were diluted 100-fold before GSD analysis.

2. Per the revised draft guidance on cyclosporine[4], the firm conducted statistical analysis using the earth movers distance (EMD) method to demonstrate equivalence between the test and RLD formulations in the shape of the globule size distribution profile. Based on the firm's analysis (see above table), test product is bioequivalent to the RLD.

3. The reviewer did not conduct statistical analysis as the firm did not submit SAS transport files to assess the difference (in terms of distance) between the shapes of globule size distribution profiles of the test product and RLD. The firm will be requested to submit this information.

4. The pivotal GSD study is **inadequate**.

5. **Deficiencies Related To Pivotal In Vitro Release Testing (IVRT) Study**

Deficiency 8: *Your pivotal IVRT study is inadequate as you did not submit IVRT method development and validation report. Therefore, the submitted IVRT data using rotating bottle dissolution apparatus is not suitable to evaluate the comparative in vitro release testing of the test product and the RLD. Please submit complete IVRT method development and validation report as outlined below.*

Firm's response: Mylan acknowledges Agency's comment. Please note that the IVRT method development report enclosed in this submission clearly describes the suitability of bottle rotating apparatus to evaluate the comparative in-vitro release testing of the Cyclosporine Ophthalmic Emulsion. Also, IVRT method validation report VR-136; Supplement-01; Version-00 titled "Partial validation for determination of in vitro release of cyclosporine in cyclosporine ophthalmic emulsion 0.05% by using high performance liquid chromatography" is enclosed in Section 1.12.15.

Reviewer's comment:
In the current submission, the firm submitted IVRT method development and validation report, demonstrating the suitability of rotating bottle dissolution apparatus to evaluate comparative in vitro release of the test product and the RLD. The firm's response is adequate.

Deficiency 9: *You conducted the IVRT study at 37°C, and the aliquots for analysis were collected after the test and reference samples reached room temperature. It appears, however, that you did not measure the temperature of the samples while collecting the aliquots. Please confirm that all the samples were at the same temperature when the aliquot was collected. In addition, please justify why the samples were allowed to reach room temperature before subsequent analysis.*

Firm's response: Mylan would like to clarify to the Agency that there was an inadvertent error in the sample preparation procedure. The analytical procedure erroneously mentioned "*After the specified time (5, 10, 30, 60, 120, 180, 240 min) the centrifuge tubes were removed and allowed them to stand for 2 minutes to attain the room temperature*" instead of "*After the specified time (5, 10, 30, 60, 120, 180, 240 min) the centrifuge tubes were removed and allowed them to stand for 2 min at room temperature*". We apologize for this inadvertent error. Please note that an errata to correct the aforementioned text is enclosed along with the copy of test procedure in Section 1.12.15. (b) (4) [redacted]

Reviewer's comment:
The firm stated that there was an inadvertent error in the SOP which has now been corrected to reflect that all samples were allowed to stand at room temperature for 2 min (b) (4) [redacted]. The firm's response is adequate.

Deficiencies Related to In Vitro Release Testing (IVRT) Method Development

Deficiency 10A: *Your pre-study IVRT method development is inadequate. Please submit the IVRT method development report which should contain information including, but not necessarily limited to, the following: Discriminatory capability of the method [Please provide experimental data showing the ability of your proposed dissolution method to discriminate the effect of process variability in the production of test formulations. Please refer to the revised Draft Guidance on Cyclosporine Ophthalmic Emulsion (revised in October 2016) for the Agency's recommendation in this regard.*

Firm's response: As requested by the Agency, Mylan is hereby providing the experimental data to show the ability of our proposed dissolution method to discriminate the effect of process variability in the production of Cyclosporine Ophthalmic Emulsion. A copy of IVRT method development report is enclosed in Section 1.12.15.

Reviewer's comment

The firm submitted IVRT method development report demonstrating the discriminatory capability of the method. The IVRT method development results and data are adequate. The firm's response is adequate. The data is reviewed below:

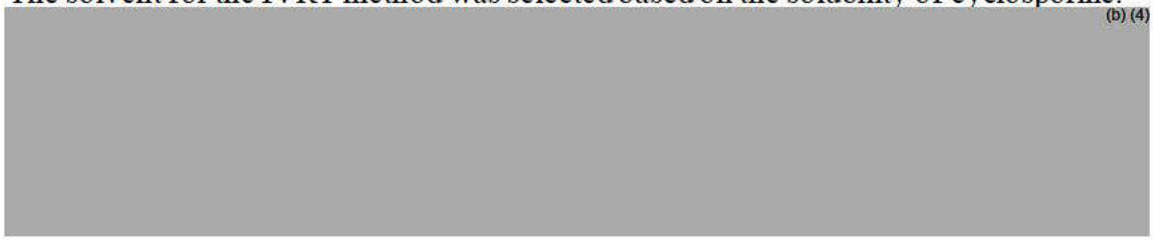
The data above indicates that the drug release profile for test batch no. 2212-009B is different from test batch no. 1138- 130 and the RLD (#81028). These two batches were manufactured with different process parameters. In vitro release profile of the test batch 1138-130 was found to be similar to the RLD. The above data clearly demonstrates that the in vitro drug release method is capable of discriminating the batches manufactured with variation in the process parameters. The firm's response is adequate.

Deficiency 10B: *Please justify with experimental data the selection of the apparatus, release medium, dilution medium, rotation speed of the IVRT method, and sample amount.*

Firm's response: Please note that the experimental data demonstrating the selection of sample amount, release medium, dilution medium and rotation speed of the proposed IVRT method is described in IVRT method development report under section 3. The report is enclosed in Section 1.12.15.

Reviewer's comment:
The firm submitted IVRT method development report justifying with experimental data the selection of the release medium, IVRT apparatus, dilution medium, rotation speed of the IVRT method, and sample amount. The IVRT method development results and data are adequate. The firm's response is adequate. The data is reviewed below:

Selection of solvent
The solvent for the IVRT method was selected based on the solubility of cyclosporine.



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(b) (4)

Based on above IVRT development studies, the firm selected the final IVRT method using the rotating bottle dissolution apparatus. The method parameters are shown below:

Table 11. Final *in vitro* release test parameters

Product	**Cyclosporine Ophthalmic emulsion**
Apparatus	Bottle rotating
Dissolution medium and volume	Isobutyl acetate, 3 mL
Rotation speed	75 RPM
Sample amount	1 g (=1ml)
Temperature	37 °C
Sampling Time point	5, 10, 30, 60, 120, 180 and 240 min.
Sampling volume	0.1 mL

(b) (4)

(b) (4)

Deficiencies Related to In Vitro Release Testing (IVRT) Method Validation

Deficiency 11A: *Your pre-study IVRT method validation is inadequate. Please submit the IVRT method validation report which should contain information including, but not necessarily limited to, the following: Evaluation of repeatability, intermediate precision, receptor solution stability, and recovery.*

Firm's response: As requested by the Agency, analytical method validation for determination of in-vitro release of cyclosporine from the drug product, 0.05% for required validation parameters viz. repeatability, intermediate precision, receptor solution stability, and recovery is performed. A copy of the partial method validation report no. VR-136, Supplement-01 (version-00) is enclosed in Section 1.12.15.

Reviewer's comment:
The firm submitted IVRT method validation report demonstrating repeatability, intermediate precision, receptor solution stability, and recovery. The results are discussed below. The IVRT method validation report, demonstrating method precision, intermediate precision, stability and recovery of cyclosporine is adequate. The firm's response is adequate.

(b) (4)

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(b) (4)

Deficiency 11B: *Please submit evaluation of IVRT method robustness [should include, at minimum, temperature and pH of the dissolution medium].*

Firm's response: As requested, robustness of IVRT method for determination of in vitro release of cyclosporine has been evaluated for the following parameters.

- Variation in RPM of the bottle rotating apparatus
- Variation in temperature of bottle rotating apparatus
- Variation in volume of dissolution medium.

Please note that the pH of dissolution medium was not considered as a parameter to conduct robustness study as the dissolution medium (Isobutyl Acetate) is non-aqueous in nature, therefore there is no significance of pH.

Reviewer's comment:

The firm submitted IVRT method validation report demonstrating robustness of the IVRT method (variation in speed, temperature of the apparatus and volume of dissolution medium). The results are discussed below. The firm did not consider pH for robustness studies as the dissolution medium is non-aqueous in nature. The IVRT method validation report, demonstrating method robustness is adequate. The firm's response is adequate.

(b) (4)

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Deficiency 12: *For your GSD and IVRT studies, you did not submit study design and product information summary tables. Please provide all information in tabular format.*

Firm's response: As requested by the Agency, study design and product information summary tables including all the appropriate information for GSD study and IVRT study are enclosed in Section 2.7.1.

Reviewer's comment:
The firm submitted study design and product information summary tables for GSD and IVRT studies. The firm's response is adequate.

Study design summary table for IVRT study

Study design and product information summary for IVRT study	
Study No.	CPS-IVR Part-IV
Study site	Mylan Laboratories Ltd., Clinical Research Centre, Saradhi Chambers, Plot No: A- 4, Rukminipuri, Dr A.S.Rao Nagar, Hyderabad-500062, Telangana, India.
Principal Investigator	Mr. Amarnath Jaiswal
Study Dates& Sample Analysis Dates*	21/09/2013 to 22/09/2013
SOP No.	Analytical Method Procedure no: AMP-136-00 is used for the determination of In vitro release rate
SOP Effective Date	16/09/2013
SOP Title	Determination of In Vitro Release of Cyclosporine in Cyclosporine Ophthalmic Emulsion 0.05% by HPLC
Testing Method Description	In vitro release rate test
Testing Equipment Used (e.g., name, model, etc.)	(1) Bottle rotating dissolution apparatus (2) (b) (4) (b) (4) HPLC)
Operating Conditions for Testing Equipment Used	Equipment's used in the study were well within the calibration duration. Bottle rotating dissolution apparatus Calibration done on:13-09-13 Bottle rotating dissolution apparatus Calibration due on :12-12-13
	HPLC Calibrated done date(Instrument ID's: CRC/BL/420 & 424): 03-07-2013 & 23-07-2013 respectively HPLC Calibration due date (Instrument ID's: CRC/BL/420 & 424): 02-01-2014 & 22-01-2014 respectively
Analytical method Description	The analytical method was used for comparative in vitro drug release study of Cyclosporine Ophthalmic emulsion 0.05% on test product (Mylan) and reference product RESTASIS®
* This is the date when experiment was performed.	

Product information summary table for IVRT study

Product	Test	Reference
Treatment ID	NA	NA
Product Name	Cyclosporine Ophthalmic Emulsion 0.05%	RESTASIS®
Manufacturer	(b) (4)	Allergan Inc, Irvine, CA92612, USA
Batch/Lot No.	01813A	80773
Manufacture Date	Jul-13	Not available
Expiration Date	NA	Apr-15
Strength	0.05%	0.05%
Dosage Form	Ophthalmic emulsion	Ophthalmic emulsion
Exhibit batch Size	(b) (4)	NA
Production batch size		NA
Potency	01813A: 99.1%	NA
Content uniformity (mean, AV)	NA	NA
Dose administered	NA	NA
Route of administration	NA	NA

NA: Please Note, Mylan wishes to establish bio-equivalence using option 1 i.e. In-Vitro Option, accordingly the information which is mentioned as NA, is deemed not necessary

Study design summary table for GSD study

Study design and product information summary for GSD study	
Study No.	CPS-CRT Part-II
Study site	Mylan Laboratories Ltd., Clinical Research Centre, Saradhi Chambers, Plot No: A- 4, Rukminipuri, Dr A.S.Rao Nagar, Hyderabad-500062, Telangana, India.
Principal Investigator	Mr. Amarnath Jaiswal
Study Dates & Sample analysis date*	11/09/2013, 12/09/2013 & 13/09/2013
SOP No.	Analytical Method Procedure no: AMP-134-00 is used for the determination of Globule Size distribution
SOP Effective Date	6/9/2013
SOP Title	Determination of globule size distribution of Cyclosporine ophthalmic emulsion using Zetasizer Nano series (Nano-ZS)
Testing Method Description	Globule Size distribution (Z-Average and PDI)
Testing Equipment Used (e.g., name, model, etc.)	Zetasizer Nano ZS
Operating Conditions for Testing Equipment Used	Equipment used in the study was well within the calibration duration. Zetasizer Calibration done on:30-08-13 Zetasizer Calibration due on :29-08-14
Analytical Method Description	The analytical method was used for comparative study of Globule Size distribution (Z-Average and PDI) of Cyclosporine Ophthalmic emulsion 0.05% on test product (Mylan) and reference product RESTASIS®
* This is the date when experiment was performed.	

Product information summary table for GSD study

Product	Test	Reference
Treatment ID	NA	NA
Product Name	Cyclosporine Ophthalmic Emulsion 0.05%	RESTASIS®
Manufacturer	(b) (4) Mfg for: Mylan Laboratories	Allergan Inc, Irvine, CA92612, USA
Batch/Lot No.	01813A, 01813B, 03912A	80773, 80796, 81028
Manufacture Date	July 2013, July 2013, Nov 2012 respectively	NA
Expiration Date	NA	April 2015 for all the batches
Strength	0.05%	0.05%
Dosage Form	Ophthalmic emulsion	Ophthalmic emulsion
Exhibit batch Size	(b) (4)	NA
Production batch size		NA

Potency	01813A,: 99.1%	NA
	01813B : 99.1 %	NA
	03912A : 95.7%	NA
Content uniformity (mean, AV)	NA	NA
Dose administered	NA	NA
Route of administration	NA	NA

NA: Please Note, Mylan wishes to establish bio-equivalence using option 1 i.e. In-Vitro Option, accordingly the information which is mentioned as NA, is deemed not necessary

4.2 Pivotal IVRT Study

Sample analysis calibration and quality control

Pivotal IVRT study No. CPS-IVR Analyte: Cyclosporine								
Parameter	**Standard Curve Samples**							
Concentration (µg/mL)	CS 1	CS 2	CS 3	CS 4	CS 5	CS 6	CS 7	CS 8
	0.50	1.0	1.12	2.4	4.7	7.4	9.6	12.5
Inter day Precision (%CV)	3.96	5.05	7.53	3.01	1.71	1.80	1.2	1.05
Inter day accuracy (%Actual)	104.1	95.6	95.8	97.2	100.5	101.7	103.0	101.7
Linearity	0.991-0.999							
Linearity Range (µg/mL)	0.5 – 12.5							
LOQ (µg/mL)	0.5							

Pivotal IVRT study No. CPS-IVR Analyte: Cyclosporine			
Parameter	**Quality Control Samples**		
	LQC	**MQC**	**HQC**
Concentration (µg/mL)	1.5	4.6	9.1
Inter day Precision (%CV)	6.9	2.2	0.9
Inter day accuracy (%Actual)	99.8	101	101

Reviewer's Comments:

- Sample analysis was conducted using a validated high-performance liquid chromatography (HPLC) method.

- No samples were reanalyzed.

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Reviewer calculated f2 value between 3 batches of the test and RLD products		
Test product batch#	RLD batch#	f2 value
01813B	80796	63.8
03912A	80773	58.4
01813A	81028	52.5

Reviewer's Comments:

- Based on the data submitted in the IVRT method development and validation report, rotating bottle dissolution apparatus is suitable to evaluate the comparative in vitro release testing of the test product and the RLD.

- To capture early and complete drug release from the test product and the RLD, the firm determined drug release at both early and later time points (from 5 min through 240 min). At each time point after sample collection, sampling volume (0.1 mL) was replaced with equal volume of fresh dissolution media.

- In accordance with the draft guidance for cyclosporine, the IVRT method is discriminatory and captures the gradual drug release from the test product and the RLD.

- The firm calculated cumulative percentage drug release *vs*. time for 3 batches each of the test product and RLD and compared the drug release profiles by calculating the f_2 value. Demonstrating similarity in drug release profile between the test product and RLD is in agreement with the consult response from ORS[3].

- Based on the above table, the drug release profile is similar (f_2 value>50) between each of the 3 batches of the test product and RLD. The reviewer calculated f_2 values are in agreement with the values reported by the firm.

- The pivotal IVRT testing is **adequate**.

Deficiencies Related to Physicochemical Characterization

Deficiency 13: *With regard to your physicochemical characterization data, please provide viscosity profile as a function of applied shear instead of single point viscosity data you provided with this submission. In addition, please provide information on drug distribution in different phases within the formulation. Please refer to the revised draft guidance on Cyclosporine ophthalmic emulsion (October 2016) for Agency's recommendation on comparative physicochemical characterization studies.*

Firm's response: It may be noted that comparative data for viscosity profile as a function of applied shear for the proposed product and RLD has been provided as part of response to Product Quality; FDA Comment 5 above. Additionally, Mylan would like to note that information on drug distribution in different phases within formulation has already been submitted as part of the amendment submitted on July 21, 2016 (Sequence No. 0024) in support of the additional comparative physicochemical characterization data as recommended in the revised draft FDA Bioequivalence guidance published in February 2016.

Reviewer's comment:
The firm submitted comparative viscosity profile as a function of applied shear and drug distribution in different phase's data. This data will be reviewed by the Office of Pharmaceutical Quality (OPQ, refer to section 4.4 for further details). The firm's response is adequate.

Deficiency 14: *All of your exhibit batches should be at least 1/10 the size of the commercial batch and the manufacturing process used for the three exhibit batches should be reflective of the process used for the commercial batch. Please refer to the revised draft guidance on Cyclosporine ophthalmic emulsion (October 2016) for Agency's recommendation on the size of the exhibit batches.*

Firm's response: Mylan acknowledges the Agency's comment. Please note that the submitted exhibit batch as well as commercial batch size is of (b) (4)

Reviewer's comment:
The exhibit and commercial batches are of the same size (b) (4)). The firm's response is adequate.

4.3 Attachments

ORS Consult for ANDA (b) (4)	ORS Consult .docx
Meeting minutes from Jan 27, 2016 for ANDAs (b) (4)	Meeting Minutes Jan_27_2016 ver 3.d

Consult response from DTP	DTP Consult response_ANDA 205
Consult response from DQMM	20160629_Mylan_Consult_response_final.
DPQR report on GSD testing of cyclosporine ophthalmic emulsion	DPQR Report on GSD Testing.pdf

Email from RPM: This is a potential first generic. There was some kind of filing issue where the cyclosporines were RTR and then rescinded and this falls in that. Policy is currently trying to sort out which would qualify as first filers, if any. This is a pretty complicated situation.

4.4 Background

On 11/25/2015, upon DBI's request, a meeting with the OPQ, the Office of Testing and Research (OTR) and ORS was held to discuss the approach for evaluating issues associated with Cyclosporine ophthalmic emulsion applications. Further action plans were made among disciplines (for details see meeting minutes)[6].

In October 2016, the Office of Generic Drugs (OGD) posted a revised Draft Guidance on Cyclosporine ophthalmic emulsion. According to this draft guidance, the test product should;

- Q1/Q2 the same as the RLD.
- Have comparable physicochemical properties including GSD, viscosity profile as a function of applied shear, pH, zeta potential, osmolality, surface tension and drug distribution in different phases within the formulation.
- Have acceptable comparative in vitro drug release rate tests.

In March 2016, through email communication with the Division of Biopharmaceutics within OPQ[7], it was confirmed that OGD does not need to review the IVRT data with respect to establishing a quality control method and specification at this time (except to check that IVRT data were submitted). In the same email trail, it was confirmed that OGD's review responsibilities for Cyclosporine Ophthalmic Emulsion applications are:

- Q1/Q2 sameness between the Test and Reference formulations (also reviewed by OPQ).

[6] \\cdsnas\ogds11\DIVISION\BIO\BIO1\Meeting Minutes\DBI non-Bio Management Meeting\2016\11252015 Cyclosporine Ophthalmic Emulsion Meeting Minutes.docx.

[7] (b) (4)

- Comparative Globule Size Distribution (GSD) data.
- IVRT with respect to establishing BE.

OPQ will review all comparative physicochemical characterizations except GSD.

NOTE TO REGULATORY PROJECT MANAGER (RPM): A routine inspection of the analytical portion for the in vitro studies will be requested for the current application.

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 205894

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Cyclosporine Ophthalmic Emulsion, 0.05%

The Division of Bioequivalence III (DB III) has completed its review of your response to the complete response (CR) letter dated December 08, 2016 and has identified the following deficiency (*to be communicated as easily correctable deficiency*):

For your pivotal globule size distribution (GSD) study (No. CPS-CRT), please submit SAS transport files to assess the difference (in terms of distance) between the shapes of globule size distribution profiles for each of the 3 lots of the test (Nos. 01813A, 01813B, 03912A) and RLD (Nos. 80773, 80776, 81028) products. SAS transport files for the shape of the globule size distribution profiles should be submitted for undiluted and serially diluted samples (25-, 50-, 100-, and 200-fold dilution) for Agency's evaluation.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 Outcome Page

Completed Assignment for 205894 ID: 31204

Reviewer: Chimalakonda, Krishna **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Items:

D	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*		
31204	2/8/2017	BIO	ANDA Amendment [1]	1	1	Edit	Delete
31204	2/8/2017	Complexity	Droplet/Globule/Liposome/Particle Size Distribution [1]	1	1	Edit	Delete
31204	2/8/2017	Complexity	First Generic Drug Product Review [1]	1	1	Edit	Delete
31204	2/8/2017	Complexity	In vitro Release Test (IVRT) [0.5]	0.5	0.5	Edit	Delete
312 4	2/8/2017	Para lel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1	Edit	Delete
312 4	2/8/2017	Para lel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1	Edit	Delete
31204	2/8/2017	Parallel	Waiver Ophthalmic Solution [1]	1	1	Edit	Delete
31204	5/31/2017	BIOQUALITY	Quality Assessment [1-5]	4.75	4.75	Edit	Delete
				Total:	11.25		

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	205894
Drug Product Name	Cyclosporine Ophthalmic Emulsion
Strength(s)	0.05%
Applicant Name	Mylan Pharmaceuticals
Applicant Address	781 Chestnut Ridge Road, Morgantown, WV 26505
Applicant's Point of Contact	Joseph J. Sobecki, 781 Chestnut Ridge Road, Morgantown, WV 26505
Contact's Telephone Number	304-599-2595
Contact's Fax Number	304-285-6407
Contact's Email	Joseph. Sobecki@mylan.com
Original Submission Date(s)	11/01/2013
Submission Date(s) of Amendment(s) Under Review	07/10/2015 (Additional BE data submitted by the firm)
First Generic	Potential first generic (see section 5.9)
Primary Reviewer	Krishna Chimalakonda, Ph.D.
Secondary Reviewer	Svetlana Cherstniakova, Ph.D
Tertiary Reviewer	April C. Braddy, Ph.D
Study Number (s)	CPS-CRT
Study Type (s)	Comparative Physicochemical Characterization
Strength (s)	0.05%
Analytical Site	Mylan Laboratories Clinical Research Center, Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India
Study Number (s)	CPS-CRT-00
Study Type (s)	Determination of Globule Size Distribution
Strength (s)	0.05%
Analytical Site	Mylan Laboratories Clinical Research Center, Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India
Study Number (s)	CPS-IVR-00
Study Type (s)	Comparative In Vitro Drug Release Testing
Strength (s)	0.05%
Analytical Site	Mylan Laboratories Clinical Research Center, Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☒ **Pending** ☐ **Complete** **Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
Biowaiver	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **Not applicable**

QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ Not applicable		
Formulation	☒ Adequate ☐ Inadequate		
Overall Review Result	☐ Adequate ☒ Inadequate		
Revised/new Draft Guidance Included	☐ YES ☒NO		
Communication	☐ ECD ☐ IR ☒ Not Applicable		
Deficiency Classification	☒ Major (Deficiencies to be communicated by CR) ☐ Minor ☐ N/A (Review is Adequate)		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 13	**Formulation Q1/Q2**	**0.05%**	**ADEQUATE**
1, 13	**Globule Size Distribution**	**0.05%**	**INADEQUATE**
1, 13	**In vitro Release Testing**	**0.05%**	**INADEQUATE**
1, 13	**Waiver**	**0.05%**	**INADEQUATE**

1 EXECUTIVE SUMMARY

Mylan Pharmaceuticals has requested a waiver of *in vivo* bioequivalence (BE) studies for its test product, Cyclosporine Ophthalmic Emulsion, 0.05% under 21 CFR § 320.24 (b)(6). The reference listed drug (RLD) product is Restasis® (cyclosporine) Ophthalmic Emulsion, 0.05% (NDA 050790) manufactured by Allergan Inc.

Based on the draft guidance for Cyclosporine Emulsion/ophthalmic (Oct. 2016)[1], in order *to qualify for the in vitro option for this drug product—pursuant to 21 CFR 320.24 (b)(6), under which "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product— all of the following should be met:*

i. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[2] and quantitatively (Q2)[3] the same.

ii. The comparative physicochemical characterizations of the test and RLD formulations. The comparative study should be performed on at least three exhibit lots of both test and RLD products[4].

iii. Acceptable comparative in vitro drug release rate testing (IVRT) of cyclosporine from the test and RLD formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.

In the current application, the test product and the RLD contain the same amount of active and inactive ingredients in the same concentrations. The test formulation is Q1/Q2 the same as the RLD.

To demonstrate bioequivalence (BE), the firm submitted data on the comparative globule size distribution (GSD) using dynamic light scattering (DLS) and IVRT using rotating bottle dissolution apparatus. A consultation[5] was sent to the Office of Research Standards (ORS) to seek clarification on the acceptability of the comparative GSD and IVRT data. Based on the submitted data, ORS[6, 7] concluded that the pivotal GSD and IVRT studies

[1] Draft Guidance on Cyclosporine: Last accessed on 10/18/2016 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf

[2] Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.

[3] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

[4] All 3 exhibit batches should be at least 1/10 the size of the commercial batch and the manufacturing process used for the 3 exhibit batches should be reflective of the process used for the commercial batch.

[5] GDRP ANDA 205894-Orig-1, Consult to ORS, Krishna Chimalakonda, 05/26/16. Last accessed date: 08/16/2016

[6] GDRP ANDA 205894-Orig-1, ORS/DTP consult response, Mohammad Absar, 08/11/16. Last accessed date: 08/16/2016

are inadequate. The firm will be requested to address the following deficiencies, in addition to providing information as outlined in the revised drug product specific guidance document:

- Clarify which GSD data are from the test and reference samples.
- Based on the revised draft guidance[1], additional data should be submitted to demonstrate equivalence between the test and RLD formulations in the shape of the globule size distribution (such as the presence of multiple peaks). See section 5.9 for the ORS consult response.
- Submit comparative GSD data and size distribution profiles (histograms) for both undiluted samples and upon dilution of the test product and RLD.
- Repeat GSD method validation using RLD samples.
- Submit pre-study method development and validation report for the IVRT study.

The firm submitted comparative physiochemical characterization data (pH, osmolality, viscosity, zeta potential and surface tension) for both test and RLD products, which will be further evaluated by OPQ.

There are multiple Office of Scientific Integrity and Surveillance (OSIS) inspections for the analytical site used in the current application. However, all the studies inspected by OSIS at the analytical site pertain to inspection of the analytical portion of fasting and fed BE studies. There is no inspection history for the analytical site which is related to IVRT and GSD studies. Therefore, the OSIS inspection history for the analytical site used in the current ANDA is not relevant to the studies conducted in the current submission. A routine inspection of the analytical portion of the study will be requested for the current ANDA after the firm submits the above requested *in vitro* BE study data. Therefore, the overall OSIS inspection status for the current ANDA is considered PENDING at this time.

The Division of Bioequivalence III (DBIII) does not grant the waiver request due to major deficiencies related to GSD and IVRT studies and pending OSIS inspection of the analytical site.

The application is **inadequate** with deficiencies.

[7] GDRP ANDA 205894-Orig-1, ORS/DQMM consult response, Meng Hu, 06/30/16. Last accessed date: 08/17/2016

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3 BACKGROUND

On 11/25/2015, upon DBI's request, a meeting with the OPQ, the Office of Testing and Research (OTR) and ORS was held to discuss the approach for evaluating issues associated with Cyclosporine ophthalmic emulsion applications. Further action plans were made among disciplines (for details see meeting minutes)[8].

In February 2016, the Office of Generic Drugs (OGD) posted a revised Draft Guidance on Cyclosporine ophthalmic emulsion[1]. According to this draft guidance, the test product should;

- Be Q1/Q2 the same as the RLD.
- Have comparable physicochemical properties including GSD, viscosity profile as a function of applied shear, pH, zeta potential, osmolality, surface tension and drug distribution in different phases within the formulation.
- Have acceptable comparative in vitro drug release rate tests.

In March 2016, through email communication with the Division of Biopharmaceutics within OPQ[9], it was confirmed that OGD does not need to review the IVRT data with respect to establishing a quality control method and specification at this time (except to check that IVRT data were submitted). In the same email trail, it was confirmed that OGD's review responsibilities for Cyclosporine Ophthalmic Emulsion applications are:

- Q1/Q2 sameness between the Test and Reference formulations (also reviewed by OPQ).
- Comparative Globule Size Distribution (GSD) data.
- IVRT with respect to establishing BE.

OPQ will review all comparative physicochemical characterizations except GSD.

On 5/26/2016, DBIII sent consult request[5] to OGD/ORS/DTP and OGD/ORS/DQMM for the current ANDA with questions regarding the GSD and IVRT studies. On 6/30/2016 and 08/11/2016, DQMM[6] and DTP[7] provided their consult response, respectively. Please note that the consult response will be reviewed separately. The current BE reviewer concurs with the ORS consult findings which are reflected in this review.

[8] \\cdsnas\ogds11\DIVISION\BIO\BIO1\Meeting Minutes\DBI non-Bio Management Meeting\2016\11252015 Cyclosporine Ophthalmic Emulsion Meeting Minutes.docx.

[9] (b) (4)

4 SUBMISSION SUMMARY

4.1 Drug Product Information[10]

Test Product	Cyclosporine Ophthalmic Emulsion, 0.05%
Reference Product*	Restasis® (cyclosporine) Ophthalmic Emulsion, 0.05%
RLD Manufacturer	Allergan Inc.
NDA No.	050790
RLD Approval Date	12/23/2002
Indication[11]	RESTASIS® is a topical immunomodulator indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

4.2 PK/PD Information[11]

Bioavailability	Blood concentrations of cyclosporine, in all the samples collected, after topical administration of RESTASIS® 0.05%, twice daily, in humans for up to 12 months, were below the quantitation limit of 0.1 ng/mL. There was no detectable drug accumulation in blood during 12 months of treatment with RESTASIS® ophthalmic emulsion.
Food Effect	Not applicable for ophthalmic drug product
Tmax	Not provided in the RLD labeling
Metabolism	Not provided in the RLD labeling.
Excretion	Not provided in the RLD labeling.
Half-life	Not provided in the RLD labeling.
Dosage and Administration	Invert the unit dose vial a few times to obtain a uniform, white, opaque emulsion before using. Instill one drop of **RESTASIS®** ophthalmic emulsion twice a day in each eye approximately 12 hours apart. **RESTASIS®** can be used concomitantly with artificial tears, allowing a 15 minute interval between products. Discard vial immediately after use.
Maximum Daily Dose	One drop twice a day.
Drug Specific Issues (if any)	N/A

[10] Electronic Orange Book, last accessed on 04/29/2016.
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=050790&TABLE1=OB_Rx
[11] RLD label: Drugs@FDA: last accessed on 04/29/2016
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050790s021lbl.pdf

4.3 OGD Recommendations for Drug Product[12]

Number of studies recommended:	2 Options: In Vitro or In Vivo Study	
Waiver request of in-vivo testing:	Yes.	
Source of most recent recommendations:	Draft Guidance on Cyclosporine (Recommended Jun 2013; Revised Feb. 2016 and Oct. 2016)  Latest Cycloporine Guidance.pdf	
Summary of OGD or DB History	Pending ANDAs (Not Yet Reviewed)	Yes
	Approved ANDAs	No
	Previously Reviewed ANDAs	Yes
	Protocols	Yes[13] (not from the current applicant)
	Controls	Yes[14] (#11-0183 from the current applicant)
	Pending Citizen Petitions and other legal and regulatory issues	The RLD is listed in the OGD Policy Alert list.  OGD Policy Alert List_as of 08122016.

Dissolution test method and sampling times: Currently, there are no USP or FDA-recommended in vitro drug release testing methods for ophthalmic emulsion formulation.

[12] Draft Guidance on Cyclosporine: Last accessed on 10/18/2016 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf

[13] OGD Division of Bioequivalence Protocols Tracking: Search term: Cyclosporine Last accessed: 04/29/2016 http://fdswv04385/seltrack/ProtocolGrid.ASP

[14] OGD - CONTROLS (Correspondence) Document Tracking: Search term: Cyclosporine Last accessed: 04/29/2016 http://cdsogd1/controls/DOCGRID.ASP

4.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	Yes	1
In Vitro Release Testing	Yes	1
Globule Size Distribution	Yes	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

4.5 Waiver Request(s) For Ophthalmic Emulsions

Strengths for which waivers are requested, if applicable	0.05%
Waiver regulation cited?	21 CFR § 320.24 (b) (6)
Strengths considered for 21 CFR 320.24 (b)(6)	0.05%
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	No
Waivers granted?	**No**
If not then why?	Refer to the deficiency letter.

4.6 Deficiency Comments

Please refer to the deficiency letter.

4.7 Recommendations

The Division of Bioequivalence III (DBIII) does not agree that the information submitted by Mylan Pharmaceuticals, demonstrates that its test product, Cyclosporine Ophthalmic Emulsion, 0.05%, meets the requirements of Section 21 CFR § 320.24 (b) (6), along with the current DB recommendations for ophthalmic drug products, due to the deficiencies specified in the letter. The DBIII denies the waiver of bioequivalence testing.

4.8 Comments for Other OGD Disciplines

Discipline	Comment
Office of Pharmaceutical Quality (OPQ)	Please note the acceptability of this application is deferred to OPQ for reviewing the physicochemical properties.

5 APPENDIX

5.1 Formulation

Composition of the firm's test product: Cyclosporine Ophthalmic Emulsion, 0.05%

Component	0.05%			Pharmaceutical Function	Quality Standards
	Quantity (mg/mL)	% w/v	% w/w[1]		
Active Ingredient					
Cyclosporine	(b) (4)	0.05	0.05	Active	USP
Inactive Ingredients					
Castor Oil	(b) (4)			(b) (4)	NF
Polysorbate 80					NF
Glycerin					USP
(b) (4) (Carbomer Co-polymer Type A)[4]					NF
(b) (4) Sodium Hydroxide[2]				pH adjusting agent	NF
Water for Injection				(b) (4)	USP
(b) (4)					

Formulation of the RLD product (NDA050790)[15] (NOT TO BE RELEASED UNDER FOIA)

Table 2.3.P.3-2 Quantitative Composition of Cyclosporine Ophthalmic Emulsion 0.05% (formula 9054X)

Ingredient	Concentration (% w/w)	Concentration (mg/g)	Amount for a (b) (4)
Cyclosporine, USP	0.05		(b) (4)
Castor Oil, NF	(b) (4)		
Glycerin, USP			
Polysorbate 80, NFr			
Carbomer Copolymer Type A, NF			
(b) (4) Sodium Hydroxide, NF			
Purified Water, NF			
(b) (4)			

Table 1. Comparison of Test and Reference Formulations, 0.05% strength

Ingredient	Test Product	RLD	Difference [(T-R)/ R*100%]
	%w/w (mg/g)	%w/w (mg/g)	
Cyclosporine, USP	0.05	0.05	--
Castor Oil, USP		(b) (4)	
Polysorbate 80, NF			
Glycerin, USP			
Carbomer Copolymer type A			
(b) (4) Sodium Hydroxide			
Water for injection			

Note: The firm confirmed that the formulation is Q1/Q2 the same as the RLD through Control Correspondance #11-0183.

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	No
Comments on the drug product formulation:	Acceptable.

[15] EDR: NDA50790 0110(112) 10/01/2010 SUPPL-18(Manufacturing(CMC)/New/Supplement Module 2.3.P. Manufacture \\cdsesub1\evsprod\nda050790\0110\m2\23-qos\drug-product\manufacture.pdf
[16] RLD Label: Drugs@FDA, last accessed on 04/29/2016
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050790s021lbl.pdf

Reviewer's Comments:

- The amount of the active ingredient, Cyclosporine, in the test product is 0.05 mg/g (%w/w). Cyclosporine concentration in the test product is the same as the RLD and considered acceptable.

- The amounts of inactive ingredients in the test product are within ±5% of the RLD and considered acceptable.

- The test product and the RLD contain the same amount of active ingredient and inactive ingredients in the same concentrations. The firm's test product is deemed Q1 and Q2 the same as the RLD.

- The mean pH values (b) (4) from three lots of the test product are comparable to the mean pH values (b) (4) from three lots of the RLD.

- Formulation of the test product is adequate.

5.2 Batch Information

The firm submitted Globule size distribution (GSD), pH, osmolality, viscosity, zeta potential and surface tension data with three lots of the test product and the RLD and in vitro drug release testing with one lot of test product and the RLD as shown below.

Test Performed	Test Product Lot #	RLD Product Lot #
Globule size distribution	01813A (Mfg. Date: July 2013) 01813B (Mfg. Date: July 2013) 03912A (Mfg. Date: Nov. 2012)	80773 (Exp. Date: April 2015) 80796 (Exp. Date: Not available) 81028 (Exp. Date: Not available)
Viscosity		
pH		
Osmolality		
Surface Tension		
Zeta Potential		
In vitro Drug Release	01813A (Mfg. Date: July 2013)	80773 (Exp. Date: April 2015)

Reviewer's Comments

1. The firm used the same three exhibit batches of the test and RLD products to conduct GSD, pH, osmolality, viscosity, zeta potential and surface tension studies as well as one batch of the test and RLD products for in vitro drug releasing testing.

2. The comparative physicochemical characterization data of the test product and the RLD is summarized in Section 5.7.

3. The batch information is adequate.

5.3 Globule Size Distribution Study

Table 3: Study Information

Globule Size Distribution (GSD) Study	
GSD Study #	CPS-PBE
GSD Protocol # and Title	SP-CPS-PBE, Part-III, Version-00 *(Population Bioequivalence based on Z-Average and polydispersity Index (PDI) of Cyclosporine Ophthalmic Emulsion 0.05%)*
Study Site	Mylan Laboratories Clinical Research Center, Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India
Principal Investigator	Amarnath Jaiswal, M. Sc (Tech)
Analysis Dates	09/15/13 – 09/20/13
Analytical Method Protocol # and Title	AMP-134-00 (*The determination of Globule Size Distribution and Zeta Potential of Cyclosporine Ophthalmic Emulsion 0.05%.*)
GSD Testing Equipment	(b) (4) Zetasizer Nano series (b) (4)

Reviewer's Comment

1. The firm conducted GSD study using dynamic light scattering (DLS) method with the (b) (4) zetasizer nano series (b) (4) instrument. Per the ORS consult response and the current draft product guidance, DLS is the preferred method to measure GSD.

2. In the current study, the firm diluted samples from the test product and the RLD 100-fold before GSD analysis.

3. The firm did not submit the GSD method SOP (#AMP-134-00) that was effective during the conduct of the GSD study. The firm will be requested to submit this information.

4. The study information is inadequate.

5.3.1 Pre-Study Method Development and Validation for GSD Testing by Dynamic Light Scattering (DLS) using (b) (4) Zetasizer Instrument

Reviewer's Comments

1. Per the response from ORS, the firm submitted adequate validation data for the GSD method. However, the validation of the GSD method was conducted using the test product. The firm will be requested to repeat validation using the RLD.

2. Pre-study GSD method validation is **inadequate**.

5.4 Globule Size Distribution Results

Table 4. Summary of GSD Results: PBE Analysis Results on GSD Data, Firm's Calculation

Table1

	Geometric mean		Geometric Mean Ratio	Standard Deviation		SigmaT/SigmaR Ratio
Variable	Test	Reference		SigmaT	SigmaR	
Z-Average	(b) (4)					

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	95% Upper CB <0? Pass or Fail PBE
Constant	(b) (4)		Pass

Table2

	Geometric mean		Geometric Mean Ratio		
Variable	Test	Reference		95% Upper Confidence Bound	95% Upper CB < ln(1.11)? Pass or Fail BE
PDI				(b) (4)	Pass

Table3

	Geometric mean		Geometric Mean Ratio	Standard Deviation		SigmaT/SigmaR Ratio
Variable	Test	Reference		SigmaT	SigmaR	
D10						(b) (4)
D50						
D90						

Scaled	Linearized Point Estimate	95% Upper Confidence Bound	95% Upper CB <0? Pass or Fail PBE
Constant		(b) (4)	Pass
Constant			Pass
Constant			Fail

Table4

	Geometric mean		Geometric Mean Ratio		
Variable	Test	Reference		95% Upper Confidence Bound	95% Upper CB < ln(1.11)? Pass or Fail BE
Span				(b) (4)	Pass

Table 5. PBE Analysis Results of GSD Data, Calculation by ORS

PBE for D50 (log-scale)

σ_{T0}	σ_R	Scale	Point estimate of criteria	Upper limit of criteria	PASS or FAIL
				(b) (4)	FAIL

PBE for SPAN (log-scale)

σ_{T0}	σ_R	Scale	Point estimate of criteria	Upper limit of criteria	PASS or FAIL
				(b) (4)	PASS

Reviewer's Comments

1. The firm conducted GSD study on 10 samples/lot using three lots of the test product (Nos. 01813A, 01813B, and 03912A) and the RLD (Nos. 80773, 80796 & 81028). Samples were diluted 100-fold before GSD analysis.

2. Per the statistical analysis conducted by the firm, the test product is bioequivalent to the RLD based on Z-average, polydispersity index (PDl), D_{10}, D_{50}, and SPAN.

3. Per the statistical analysis conducted by ORS[7], results from the PBE analysis conducted on the entire GSD data demonstrated that the test product is bioequivalent to the RLD based on SPAN. However, the test product is not bioequivalent to the RLD based on D50. It is important to note that ORS reviewer did not conduct statistical analysis on the data submitted by the firm. The ORS reviewer used the comparative GSD data generated by DPQR[17] on 3 exhibit lots of the test product and 9 lots of the RLD using DLS and LD to perform statistical analysis.

4. Based on the revised draft guidance on cyclosporine[1], additional data should be submitted by the firm to demonstrate equivalence between the test and RLD formulations in the shape of the globule size distribution (such as the presence of multiple peaks).

5. The firm did not submit comparative GSD data and size distribution profiles (histograms) for both undiluted samples and upon dilution of the test product and the RLD. The firm will be requested to submit this information.

6. The pivotal GSD study is inadequate.

5.5 *In Vitro* Drug Release Test (IVRT)

Table 6. Study Information

In vitro Drug Release testing (IVRT)	
IVRT Study #	CPS-IVR-00
IVRT Protocol # and Title	CPS-IVR-00, Part-IV *(Comparative In- Vitro Drug Release Rate Test of Cyclosporine from Cyclosporine Ophthalmic Emulsion 0.05%)*
Study Site	Mylan Laboratories Clinical Research Center, Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India
Principal Investigator	Amarnath Jaiswal, M. Sc (Tech)
Analysis Dates	Not available
Analytical Method Protocol # and Title	AMP-136-00 (*Determination of In Vitro Release of Cyclosporine in Cyclosporine Ophthalmic Emulsion, 0.05% by HPLC*)
IVRT Testing Equipment	Rotating bottle dissolution apparatus

[17] DPQR report on GSD testing of cyclosporine ophthalmic emulsion. Please refer to section 5.9 for the full DPQR report.

Table 7. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Cyclosporine Ophthalmic Emulsion	Restasis® (cyclosporine) Ophthalmic Emulsion
Manufacturer	(b) (4) Mylan Laboratories	Allergan Inc.
Batch/Lot No.	01813A	80773
Manufacture Date	July 2013	Not applicable (N/A)
Expiration Date	Data not available	April 2015
Strength	0.05%	0.05%
Dosage Form	Ophthalmic emulsion	Ophthalmic emulsion
Bio-batch Size	Data not available	N/A
Production Batch Size	Data not available	N/A
Potency	Data not available	Data not available
Content Uniformity (mean, %CV)	Data not available	N/A
Dose Administered	Instill one drop of RESTASIS® ophthalmic emulsion twice a day in each eye approximately 12 hours apart	Instill one drop of RESTASIS® ophthalmic emulsion twice a day in each eye approximately 12 hours apart
Route of Administration	Ophthalmic	Ophthalmic

Reviewer's Comment

1. Currently there is no FDA-recommended dissolution method or USP method/apparatus for ophthalmic emulsion products.

2. The firm conducted IVRT using rotating bottle dissolution apparatus. In ANDAs (b) (4) the firms used (b) (4) for IVRT testing.

3. Cyclosporine concentration was measured using a validated HPLC method.

4. Per the consult response from ORS, the firm did not conduct method development and validation of the IVRT method. The firm will be requested to submit complete development and validation report.

5. The firm did not submit product information (bio-batch size, potency, and content uniformity) data for the test product and the RLD. The firm will be requested to submit this information.

6. The firm did not submit analysis dates of the IVRT samples. The firm will be requested to submit this information.

7. The comparative IVRT testing of the test product and the RLD is **inadequate**.

5.6 Pivotal IVRT Study

5.6.1 Pivotal In vitro Drug Release Data

Sr. No.	Test (01813A)						
	5 min	10 min	30 min	60 min	120 min	180 min	240 min
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
N	12	12	12	12	12	12	12
Average	12	18	31	49	73	87	95
SD	1.0	0.7	1.6	2.3	2.9	2.7	3.1
RSD	8.2	3.7	5.3	4.6	3.9	3.0	3.2
Sr. No.	Reference (80773)						
	5 min	10 min	30 min	60 min	120 min	180 min	240 min
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
N	12	12	12	12	12	12	12
Average	15	23	40	59	82	95	99
SD	1.0	1.3	1.9	3.0	3.7	3.1	3.0
RSD	6.7	5.7	4.8	5.1	4.5	3.2	3.0

(b) (4)

(b) (4)

Sr. No.	Time (mins)	Reference	Test	Difference (R-T)	Difference^2
		% Drug Release			
1	5				
2	10				
3	30				
4	60				
5	120				
6	180				
7	240				
N		7	7	7	7
Sum		413	365	48	376
F2		56.5			
F1		12			

(b) (4)

Reviewer's Comments:

- To capture early and complete drug release from the test product and the RLD, the firm determined drug release at both early and later time points (from 5 min through 240 min).

- In accordance with the draft guidance for cyclosporine, the method captures the gradual drug release from the test product and the RLD.

- To maintain sink condition, sampling volume was replaced with 0.1 mL of fresh dissolution media.

- The firm calculated cumulative percentage drug release *vs*. time of the test product and the RLD and compared the drug release profiles by calculating the f2 value. This is in agreement with the recommendations in the ORS consult response.

- The f2 value between the test product and the RLD as calculated by the reviewer (f2=55.4) is in agreement with the value reported by the firm (f2=56.5).

- In agreement with the ORS consult response, the firm conducted IVRT study on one batch of the test product (No. 01813A; 12 units) and the RLD (No. 80773; 12 units).

- Per the consult response from ORS, the firm did not conduct method development and validation of the IVRT method. Therefore, the IVRT data submitted by the firm using rotating bottle dissolution apparatus is not suitable to evaluate the comparative in vitro release testing of the test product and the RLD.

- The pivotal IVRT testing is **inadequate**.

5.7 Physicochemical Properties

The firm submitted pH, osmolality, viscosity, surface tension, and zeta potential. The physicochemical properties data on the RLD and test product are provided below for information purposes only.

(b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

Reviewer's Comments:

1. The mean pH values [redacted] from three lots of the test product are comparable to the mean pH values [redacted] from three lots of the RLD.

2. The mean osmolality values measured from three lots of the test product (range: [redacted] mOsm/kg) are similar to osmolality values from three lots of the RLD [redacted] mOsm/kg).

3. The mean viscosity values measured from three lots of the test product (range: [redacted] differ with viscosity values measured from three batches of the RLD (range: [redacted] The acceptability of this data will be further reviewed by OPQ.

4. The mean surface tension values measured from three lots of the test product (range: [redacted] are similar to surface tension values from three lots of the RLD [redacted]

5. The mean zeta potential values measured from three lots of the test product (range: - [redacted] are similar to zeta potential values from three lots of the RLD [redacted]

6. Per the ORS consult response, based on the recommendations in the revised draft guidance (Oct. 2016), the firm will be requested to submit additional data on (1) viscosity profile as a function of applied shear and (2) drug distribution in different phases within the formulation.

7. The physicochemical property data will be further reviewed by the Office of Pharmaceutical Quality (OPQ).

5.8 Office of Scientific Integrity and Surveillance (OSIS) Inspection Status

Analytical Site

Site Name:	Mylan Laboratories Clinical Research Center							
Site Address:	Saradhi Chambers, A4, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, India							
Application	**Inspected BE Study Type (In Vivo, In Vitro)**	**Inspection Type (Routine or For Cause)**	**OSIS EIR Review Date in DARRTS**	**Inspection Outcome (NAI, VAI, OAI)***	**Current ANDA Analytical dates**	**Dates of Analytical portion of inspected studies**	**Were the Current ANDA studies conducted within 3 1/2 years of the studies under/pending the OSIS inspection?**	**Conclusion (Relevant, Irrelevant)**
NDA 022061	In Vivo	Routine	9/12/08	NAI		N/A	N/A	Not Relevant
NDA 022141	In Vivo	Routine	8/4/08	VAI		N/A	N/A	Not Relevant
NDA 022142	In Vivo	Routine	5/6/09	Declined		N/A	N/A	Not Relevant
NDA 200793	In Vivo	Routine	6/3/10	NAI	04/10/13 – 09/20/13	N/A	N/A	Not Relevant
(b) (4)								
NDA 022282	In Vivo	Routine	10/31/11	NAI		N/A	N/A	Not Relevant
(b) (4)								
NDA 204914	In Vivo	Routine	07/24/13	NAI		N/A	N/A	Not Relevant
ANDA 204475	In Vivo	Routine	8/4/2014	NAI		N/A	N/A	Not Relevant
(b) (4)								
NDA 204311	In Vivo	Routine	10/3/14	NAI		N/A	N/A	Not Relevant
NDA 204915	In Vivo	Routine	5/12/15	NAI		N/A	N/A	Not Relevant
ANDA 202970	In Vivo	Routine	5/12/15	Cancelled		N/A	N/A	Not Relevant
ANDA 208257	In Vivo	Not listed	N/A	Pending		N/A	N/A	Not Relevant

*NAI: No Action Indicated; VAI: Voluntary Action Indicated; OAI: Official Action In

There are multiple Office of scientific integrity and surveillance (OSIS) inspections for the analytical site used in the current application. However, all the studies inspected by OSIS at the analytical site pertain to inspection of the analytical portion of fasting and fed BE studies. There is no inspection history for the analytical site which is related to the analytical portion characterizing physicochemical properties of drug products. Therefore, the OSIS inspection history for the analytical site used in the current ANDA is not relavent to the studies conducted in the current submission. A routine inspection of the analytical portion of the study will be requested for the current ANDA. The OSIS inspection status for the current ANDA is considered pending at this time.

5.9 Attachments

ORS Consult for ANDA (b) (4)	ORS Consult .docx
Meeting minutes from Jan 27, 2016 for ANDAs (b) (4)	Meeting Minutes Jan_27_2016 ver 3.d
Consult response from DTP	DTP Consult response_ANDA 205
Consult response from DQMM	20160629_Mylan_Consult_response_final.
DPQR report on GSD testing of cyclosporine ophthalmic emulsion	DPQR Report on GSD Testing.pdf

Email from RPM: This is a potential first generic. There was some kind of filing issue where the cyclosporines were RTR and then rescinded and this falls in that. Policy is currently trying to sort out which would qualify as first filers, if any. This is a pretty complicated situation.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 205894

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Cyclosporine Ophthalmic Emulsion, 0.05%

The Division of Bioequivalence III (DBIII) has completed its review and has identified the following deficiencies:

In October 2016, the Agency announced the availability of a revised draft guidance entitled "Draft Guidance on Cyclosporine Ophthalmic Emulsion, 0.05%." This revised draft guidance provides updated product-specific recommendations for proposed generic drug products establishing bioequivalence (BE) to the reference-listed drug (RLD), Restasis® (cyclosporine ophthalmic emulsion), 0.05%.

Specifically, the revised guidance provides additional information on the previously recommended comparative physicochemical characterization studies as well as new recommendations on the measurement of drug distribution in different phases. The revised guidance also provides clarification on the comparative *in vitro* drug release testing. A copy of the revised Draft Guidance on Cyclosporine Ophthalmic Emulsion, 0.05% has been posted on FDA's Drug guidance page:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf

The revisions to the draft guidance are summarized below:

- Applicants are now advised to submit information on the drug distribution in different phases within the formulation in addition to the six previously identified physicochemical properties [i.e., globule size distribution (GSD), viscosity, pH, zeta potential, osmolality, and surface tension]. Information on the distribution of drug in different phases provides additional information about the formulation and its effect on drug release and bioavailability.
- The guidance has been clarified to state that applicants should measure the viscosity profile as a function of applied shear (as opposed to a single measurement).
- The laser diffraction method may not be suitable for this product since a number of laser diffraction instruments are not sensitive to accurately measure particles below 100 nm. In addition, obtaining a consistent obscuration percentage for the test and reference products could be challenging. Therefore, applicants are recommended to use dynamic light scattering method (or PCS, QELS) to measure the globule size of the test and RLD formulations, and provide comparable size distribution profiles (intensity-weighted histograms) upon serial dilutions. It appears that dynamic light scattering is the most suitable method to measure globule size of cyclosporine ophthalmic emulsion provided that the sample is adequately diluted. A

complementary method to measure globule size is not required. Please refer to the revised draft guidance on cyclosporine ophthalmic emulsion (posted in Oct. 2016) for Agency's recommendation on particle size characterization study.

- Applicants should submit information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement. This will ensure that the same method was used for globule size measurement and also that the measurement method is appropriate.
- Considering the fact that the shape of the globule size distribution of this product may not be mono-modal, the conventional population BE based on D50 and SPAN may not be sufficient to demonstrate bioequivalence. Instead, equivalence between the test and RLD formulations in the shape of the GSD (such as the presence of multiple peaks) should be demonstrated by appropriate statistical analysis. The statistical distance metric is preferred to assess the difference (or distance) between the profile shapes. One suggested approach is the earth mover's distance (EMD) method (*Yossi Rubner, Carlo Tomasi and Leonidas J. Guibas. The earth mover's distance as a metric for image retrieval. International Journal of Computer Vision, 40(2):99-121, 2000*), which seeks for minimal efforts to transform one distribution to the other on the basis of an optimization algorithm, operating on variable-length representation of the distributions. After obtaining the profile distances between the individual RLD data and the average RLD data ('RLD' – 'RLD center' distance), and the profile distances between the individual test data and the average RLD data ('TEST' – 'RLD center' distance), a statistical metric should be employed to quantify the difference between the two categories of distances. One suggested method is the population BE test (Guidance for Industry – Statistical Approaches to Establishing Bioequivalence. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf).
  These statistical evaluations will ensure that the globule size distributions are equivalent in shape and magnitude.
- The guidance has been clarified to state that all three exhibit batches should be at least 1/10 the size of the commercial batch and the manufacturing process used for the batches should be representative of the process used for the commercial batch.
- The guidance has been clarified to state that the methodology used for in vitro drug release testing (IVRT) should be able to discriminate the effect of process variability in the production of the test formulation. This recommendation is included to ensure that the comparative study on the drug release is conducted using a sensitive method.

Consistent with 21 CFR 320.24(a), the scientific recommendations reflected in the revised Draft Guidance on Cyclosporine Ophthalmic Emulsion represent FDA's determination of the most accurate, sensitive, and reproducible approach for conducting bioequivalence testing. Please submit all of the requested data as outlined in the current individual guidance document.

Based on the above, we also note the following deficiencies:

Deficiencies Related to Globule Size Distribution (GSD) Testing

1. Your pivotal GSD study is inadequate due to deficiencies outlined below. Please submit additional GSD data based on the revised draft guidance on Cyclosporine

ophthalmic emulsion, 0.05% (October 2016, please refer to the link above) for Agency's recommendation on comparative GSD testing.

2. Based on the revised draft guidance, additional data should be submitted to demonstrate equivalence between the test and RLD formulations in the shape of the globule size distribution (such as the presence of multiple peaks). Considering the multi-modal nature of cyclosporine globule size distribution, please use a high resolution method (such as narrow mode) that is capable of separating individual peaks.
3. Your GSD method validation is inadequate as validation data was generated using the test product. Please repeat GSD method validation using only the RLD samples. Accuracy determination should be evaluated using reference standard particles.
4. You provided data from individual samples on the Z-average size, PdI, D10, D50 and SPAN. Please clarify which data are from the test and reference samples. Please also compare the shape of the intensity histogram between the test and reference products. Equivalence in shape should be demonstrated by a suitable statistical method. In this regard, please also submit the raw data for the intensity histogram for the Agency's evaluation.
5. You provided comparative GSD data from 100x diluted samples. Please also provide GSD data from undiluted samples and upon serial dilution.
6. Please submit the standard operating procedure (SOP; #AMP-134-00) for the GSD method that was effective during the conduct of the GSD study.
7. Please provide the correlation decay curve for each sample. In addition, please specify the bin size/number used during the measurement. Please also specify the count rate, acquisition time, and number of channels that was used in the DLS method. We encourage you to keep these parameters fixed throughout the experiment.

Deficiencies Related to Pivotal In Vitro Release Testing (IVRT) Study

8. Your pivotal IVRT study is inadequate as you did not submit IVRT method development and validation report. Therefore, the submitted IVRT data using rotating bottle dissolution apparatus is not suitable to evaluate the comparative in vitro release testing of the test product and the RLD. Please submit complete IVRT method development and validation report as outlined below.
9. You conducted the IVRT study at 37°C, and the aliquots for analysis were collected after the test and reference samples reached room temperature. It appears, however, that you did not measure the temperature of the samples while collecting the aliquots. Please confirm that all the samples were at the same temperature when the aliquot was collected. In addition, please justify why the samples were allowed to reach room temperature before subsequent analysis.

Deficiencies Related to In Vitro Release Testing (IVRT) Method Development

10. Your pre-study IVRT method development is inadequate. Please submit the IVRT method development report which should contain information including, but not necessarily limited to, the following:

    a. Discriminatory capability of the method [*Please provide experimental data showing the ability of your proposed dissolution method to discriminate the effect of process variability in the production of test formulations. Please refer to the revised Draft Guidance on Cyclosporine Ophthalmic Emulsion (revised in October 2016) for the Agency's recommendation in this regard*].

    b. Please justify with experimental data the selection of sample amount, release medium, dilution medium and rotation speed of your IVRT method.

(b) (4)

Deficiencies Related to In Vitro Release Testing (IVRT) Method Validation

11. Your pre-study IVRT method validation is inadequate. Please submit the IVRT method validation report which should contain information including, but not necessarily limited to, the following:

    a. Evaluation of repeatability, intermediate precision, receptor solution stability, and recovery.

    b. Evaluation of IVRT method robustness [*should include, at minimum, temperature and pH of the dissolution medium*].

12. For your GSD and IVRT studies, you did not submit study design and product information summary tables. Please provide all information using the following tabular format:

Study No.	
Study site	
Principal Investigator	
Study Dates	
SOP No.	
SOP Effective Date	
SOP Title	
Testing Method Description	
Testing Equipment Used (e.g., name, model, etc.)	
Operating Conditions for Testing Equipment Used	

Analytical Method Description	
Sample Analysis Dates	

Product	**Test**	**Reference**
Treatment ID		
Product Name		
Manufacturer		
Batch/Lot No.		
Manufacture Date		
Expiration Date		
Strength		
Dosage Form		
Exhibit batch Size		
Production Batch Size		
Potency		
Content Uniformity (mean, AV)		
Dose Administered		
Route of Administration		

Deficiencies Related to Physicochemical Characterization

13. With regard to your physicochemical characterization data, please provide viscosity profile as a function of applied shear instead of single point viscosity data you provided with this submission. In addition, please provide information on drug distribution in different phases within the formulation. Please refer to the revised draft guidance on Cyclosporine ophthalmic emulsion (October 2016) for Agency's recommendation on comparative physicochemical characterization studies.
14. All of your exhibit batches should be at least 1/10 the size of the commercial batch and the manufacturing process used for the three exhibit batches should be reflective of the process used for the commercial batch. Please refer to the revised draft guidance on Cyclosporine ophthalmic emulsion (October 2016) for Agency's recommendation on the size of the exhibit batches.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these

concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5.10 Outcome Page

ANDA: 205894

Completed Assignment for 205894 ID: 28681

Reviewer: Chimalakonda, Krishna **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Items:

D	*Letter Date*	*Productivity Category*	*Sub Category*	*Sc r*	*Sub ot a*
2 81	1 1/20	BIO	ANDA Original [1]	1	1
2 81	1 1/20	Complexity	Droplet/Globule/Liposome/Particle Size Distribution [1]	1	1
2 81	1 1/20	Complexity	First Generic Drug Product Review [1]	1	1
2 81	1 1/20	Complexity	In vitro Release Test (IVRT) [0.5]	0.	0.5
28681	11/1/2013	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1
28681	11/1/2013	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1
2 81	1 1/20	Parallel	Waiver Ophthalmic Solution [1]	1	1
2 81	1 1/20	BIOQUALITY	Quality Assessment [1-5]	5	5
				To al :	11

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205894Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

QUALITY ASSESSMENT

MICROBIOLOGY

Product Background

ANDA: 205894-Amendment 49

Drug Product Name / Strength: Cyclosporine Ophthalmic Emulsion

Route of Administration: Topical Ophthalmic

Applicant Name: Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504

Manufacturing Site (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Theme (ANDA only): N/A

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

Review Summary:
- The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
12/17/2020	12/17/19	N/A	08/2/2021
05/26/2021	05/26/2021	N/A	08/2/2021

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
11/01/2013	1	10/13/2016
02/28/2017	2	05/28/2017
06/29/2018	3	10/15/2018
10/30/2018	3	11/1/2018

Highlight Key Outstanding Issues from Last Cycle: N/A.

Remarks: Micro was consulted to review the updates to the pending ANDA since the most recent MR03 review. (b) (4) . Priority Review has been requested.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: A205894MR01 dated 10/1/16, A205894MR02 dated 5/28/17, 205894MR03 dated 11/2/18.

List Number of Comparability Protocols (ANDA only): None

This assignment was provided to the Division of Microbiology Assessment on 8/2/2021 to meet an ODD of 8/11/21. A summary of all of the submission content to the ANDA since the last micro review (A205894MR03.doc) are included in the table below.

Submit Date	Summary of Content
7/10/19	Firm response to OGD IR regarding Q1/Q2 formulation (b) (4)
12/18/19	Firm submits email communication to Dr. Sally Choe (OGD Director) requesting meeting to resolve Agency concerns regarding drug product formulation
10/16/20	Firm submits drug product preferred formulation and two alternate formulations for FDA review.
*12/17/20	**Firm's response to FDA Product Quality CR letter dated 9/30/2020**
1/15/21	Firm Patent Amendment
1/21/21	Firm's response to FDA Bioequivalence IR email dated 1/15/2021
2/10/21	Firm Patent Amendment
2/23/21	Firm's response to FDA Bioequivalence IR dated 2/19/2021
4/1/21	Firm's response to FDA Bioequivalence IR dated 3/25/2021
*5/26/21	(b) (4)
7/15/21	Firm's response to Drug Substance IR dated 6/25/21
7/26/21	Firm's response to Drug Product IR dated 7/20/21

***Subject submission reviewed by DMA herein**

P.1 Description of the Composition of the Drug Product

(b) (4)

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Paul Dexter

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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background

ANDA: 205894-Amendment 39 and 43

Drug Product Name / Strength: Cyclosporine Ophthalmic Emulsion

Route of Administration: Topical Ophthalmic

Applicant Name: Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road,
P.O. Box 4310, Morgantown, WV 26504

Manufacturing Site (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Theme (ANDA only): Product sterility assurance

Justification (ANDA only): *N/A*

Review Summary:

- The submission is **recommended** for approval on the basis of sterility assurance.
- (b) (4). There is currently no deficiency identified based on the information submitted.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
06/29/2018	06/29/2018	N/A	10/15/2018
10/30/2018	10/30/2018	N/A	11/1/2018

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
11/01/2013	1	10/13/2016
02/28/2017	2	05/28/2017

(b) (4)

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List of Deficiencies:

There are currently no deficiencies identified based on the information provided in the submission.

Primary Microbiology Reviewer Name and Date:
Wendy Tan, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA/BII
November 2nd, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya, Ph.D.
Review Microbiologist
CDER/OPQ/OPF/DMA/BII
November 2nd, 2018

Nandini Bhattacharya

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Wendy Tan

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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background

ANDA: 205894

Drug Product Name / Strength: Cyclosporine Ophthalmic Emulsion

Route of Administration: Topical Ophthalmic

Applicant Name: Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504

Manufacturing Site (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary:

- The submission is **recommended** for approval on the basis of sterility assurance.
- (b) (4). There is currently no deficiency identified based on the information submitted.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
02/08/2017	02/08/2017	N/A	02/17/2017

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
11/01/2013	1	10/13/2016

Highlight Key Outstanding Issues from Last Cycle:

(b) (4)

Remarks: (b) (4)

Concise Description Outstanding Issues Remaining: None

Supporting Documents: None

List Number of Comparability Protocols (ANDA only): None

Wendy Tan

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Nandini Bhattacharya

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Product Quality Microbiology Review

October 13, 2016

ANDA: 205894

Drug Product Name
Proprietary: N/A
Non-proprietary: Cyclosporine Ophthalmic Emulsion

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
11/01/2013	11/01/2013	N/A	6/3/2016
07/10/2015	07/10/2015	N/A	6/3/2016
03/18/2016	03/18/2016	N/A	6/3/2016
07/21/2016	07/21/2016	N/A	7/28/2016
09/26/2016	09/26/2016	N/A	9/27/2016

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
N/A		

Applicant/Sponsor
Name: Mylan Pharmaceuticals Inc.
Address: 781 Chestnut Ridge Road
P.O. Box 4310, Morgantown, WV 26504
Representative: Joseph Sobecki, Head of Regulatory Affairs
Telephone: 304-599-2595 (b) (6)
Fax: 304-285-6407

Name of Reviewer: Wendy Tan, Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original ANDA

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product.

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Ophthalmic emulsion, topical ophthalmic, 0.05% 0.4 mL fill in a 0.5 mL LDPE single use vial in a strip of 5 vials.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Ophthalmic emulsion indicated for increasing tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS:

- This is an eCTD submission
- There are no comparability protocol in the submission
- All of the documents in the original submission (with few exceptions) have been replaced by documents submitted in the 07/10/2015 amendment

Filename: A205894MR01.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

N/A

II. Summary of Microbiology Assessments

(b) (4)

III. Product Quality Microbiology Risk Assessment

(b) (4)

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Wendy Tan

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205894Orig1s000

OTHER REVIEW(S)

Clinical Review of Comparative (Threshold) Analyses for Generic Drug Products

Division of Clinical Review (DCR)
Office of Safety and Clinical Evaluation (OCSE), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA	205894
Drug Product/Strength(s)	Cyclosporine Ophthalmic Emulsion 0.05%
ANDA Applicant	Mylan Pharmaceuticals Inc.
RLD Product Name **RLD#/Approval Date** **RLD Sponsor**	RESTASIS (Cyclosporine Ophthalmic Emulsion 0.05%) NDA 050790 / Initial Approval: December 23, 2002 Allergan
Reviewer	William Chong, MD
Submission Date	ANDA 205904, SD-60, Received January 20, 2022 ANDA 205894, SD-59, Received November 5, 2021 ANDA 205894, SD-55, Received May 26, 2021
Date of Review	January 31, 2022
Comparative Threshold Analyses Conclusion	☐ No Design Differences - Acceptable ☒ Minor Design Differences ☒ Acceptable ☐ Not acceptable ☐ Other Design Differences ☐ Acceptable ☐ Not acceptable
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)
Recommendation (see Section 4)	**Comments to the Applicant via:** ☐ OPQ Discipline Review Letter (DRL) ☐ Complete Response Letter (CRL) ☒ None
	INTERNAL Comments to: ☐ Division of Labeling Review ☐ Office of Pharmaceutical Quality

1 INTRODUCTION AND BACKGROUND

This review evaluates the drug delivery constituent part of the product and any associated product labeling and packaging. This review focuses on the analysis of the user interface[1] for the drug product comparing the proposed generic and the RLD.

1.1 Summary of Drug Product Information Pertinent to Review

The reference listed drug (RLD), RESTASIS (cyclosporine ophthalmic emulsion, 0.05%), was approved on December 23, 2002 under NDA 050790. RESTASIS is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. RESTASIS is supplied in sterile, preservative-free single-use low density polyethylene (LDPE) vials. It is intended for use by a patient or caregiver.

The latest RLD labeling, approved on July 18, 2017,[2] includes only Prescribing Information (PI) and Patient Counseling Information. The RLD does not contain an Instructions for Use (IFU). Users are instructed to instill one drop twice a day in each eye approximately 12 hours apart.

Mylan Pharmaceuticals (Mylan or the "Applicant") submitted an abbreviated new drug application (ANDA) 205894 on November 1, 2012 for Cyclosporine Ophthalmic Emulsion, 0.05%. The Applicant has received Complete Response Letters previously, most recently on September 30, 2020. A Response to Complete Response was received on December 17, 2020. The proposed product is supplied in sterile, preservative-free single-use LDPE vials. It is intended for use by a patient or caregiver.

On October 22, 2021 DCR sent an Information request (IR) letter to the Applicant requesting Mylan submit their threshold analyses comparing their proposed Cyclosporine Ophthalmic Emulsion, 0.05% to the RLD RESTASIS and high-resolution color photos of each size and strength of the to-be marketed proposed product and of each corresponding size and strength of the RLD.

1.2 Other Relevant Information

There are no pre-ANDA meeting packages or controlled correspondences for this drug product, referencing NDA 050790 as the RLD that relate to the user interface evaluation or comparative threshold analyses review.

There are currently no approved generic Cyclosporine Ophthalmic Emulsion, 0.05% products per the Orange Book.[3]

[1] User interface refers to all components of the combination product with which a user interacts.
[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050790s027lbl.pdf
[3] Orange Book search dated November 8, 2021

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW AND DISCUSSION

DCR reviewed the submitted comparative analyses of the user interface of the proposed generic product and its RLD, RESTASIS (NDA 050790).

2.1 Physical Comparison: RLD vs. Proposed

DCR examined the delivery device constituent parts of the RLD and proposed generic product using images provided by the Applicant on November 5, 2021.[4]

Table 1: Physicals Comparison of Samples – Photos of RLD and Proposed Provided by Applicant

RLD (NDA 050790)	Proposed (ANDA 205894)
Vial 	Vial 
Carton and Secondary Packaging 	Carton and Secondary Packaging 

Source: Excerpted from Response to Information Request received on November 5, 2021

The Applicant also provided the dimensions of the vials (Table 2).

[4] \\CDSESUB1\evsprod\anda205894\0055\m1\us\12-cover-letters\cover-letter-0055-information-request-response-20211105.pdf and \\CDSESUB1\evsprod\anda205894\0055\m5\53-clin-stud-rep\535-rep-effic-safety-stud\increase-tear-production\5354-other-stud-rep\gdd-doc-2021-0890\gdd-doc-2021-0890-study-report.pdf

Table 2: Comparison of Mean Dimensions of RLD and Proposed Vials Provided by Applicant

	RLD, mm (NDA 050790)	Proposed, mm (ANDA 205894)
Overall vial length	62.63	79.44
Overall vial width	12.03	12.87
Twist-off cap width	9.49	12.90
Twist-off cap length	12.10	23.17
Overall vial length without twist-off cap	50.94	66.16

Source: Adapted from Response to Information Request received on November 5, 2021

The Applicant identified the following differences:

- Difference in the shape of the vial/cap molding and overall length.
- Difference in secondary packaging with RLD using a polypropylene tray and the proposed using aluminum foil pouches and subsequently a difference in the number of vials provided in each secondary packaging.

The Applicant considers these to be minor differences.

Reviewer Comments:
I agree that there are only minor physical differences.

There are differences in the shape and dimensions of the vial. The differences in shape and dimensions do not alter the steps for opening the vial.

There is a difference in the carton and secondary packaging. The difference in the secondary packaging results in a minor difference with the RLD secondary packaging providing either 30 or 60 vials per tray while the proposed product provides 5 vials per aluminum foil pouch. The overall number of vials is the same as those available with the RLD through providing the appropriate number of foil pouches per carton.

2.2 Comparative Task Analysis: RLD vs. Proposed

The Applicant conducted a Comparative Task Analysis of the administration procedures between the proposed generic product and the RLD.[5] A tabular comparison of the general tasks provided by the Applicant is shown in table below.

Table 3: Comparison of Task Analysis

RLD (NDA 050790)	Proposed (ANDA 205894)
Open tray lid	Open carton
Remove foil seal	Open pouch
Retrieve 1 vial	Retrieve 1 vial

[5] \\CDSESUB1\evsprod\anda205894\0055\m5\53-clin-stud-rep\535-rep-effic-safety-stud\increase-tear-production\5354-other-stud-rep\gdd-doc-2021-0890\gdd-doc-2021-0890-study-report.pdf

RLD (NDA 050790)	Proposed (ANDA 205894)
Invert the unit dose a few times to obtain a uniform, white, opaque emulsion	Invert the unit dose a few times to obtain a uniform, white, opaque emulsion
Twist off cap of vial	Twist off cap of vial
Instill one drop of Restasis ophthalmic emulsion in one or both eyes	Instill one drop of Cyclosporine ophthalmic emulsion in one or both eyes
Discard vial and remaining contents immediately after use	Discard vial and remaining contents immediately after use

Source: Adapted from Response to Information Request received on November 5, 2021

The Applicant concludes that there are only minor differences in the tasks for opening the secondary packaging (i.e., opening tray lid vs. opening carton; removing foil seal of tray vs. opening foil pouches). No difference is noted in the tasks once the vial is retrieved.

Reviewer's Comments:
I agree that there are only minor differences in the tasks.

There are differences in the tasks for retrieving the vial due to differences in secondary packaging. The RLD vials can be retrieved once the foil seal of the tray has been removed. For the proposed, the vials can be retrieved once the foil pouch has been opened. With the proposed, the user would need to open additional pouches every 5 vials which is not necessary for the RLD. I agree that this is a minor difference. Opening additional pouches to retrieve vials for the proposed compared to one time opening of the tray would not necessitate additional training. Both approaches to packaging are common forms of packaging and as a result should be familiar to users and correct use would be self-evident.

I agree with the conclusion that there is no difference in the tasks once the vial is retrieved. The difference in shape and dimensions of the vials do not impact the tasks or ability to perform the tasks.

2.3 Labeling Comparison: RLD vs. Proposed

The most current RLD labeling for the single-use presentation was approved on July 18, 2017 under supplement-27. The RLD labeling includes Prescribing Information (PI) and Patient Counseling Information. **The RLD does not contain an Instructions for Use (IFU).** The RLD labeling is available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050790s027lbl.pdf.

For the labeling comparative analysis of this product, DCR conducted a review of the comparison submitted by the applicant of the relevant sections of the labeling for the RLD and the proposed generic product that relates to the use of the device, including the How Supplied section. Except for the delivery device-related part of labeling, the review of the remainder of the labeling is deferred to the Division of Labeling Review (DLR).

The Applicant performed a side-by-side comparison of their proposed carton and container labels and prescribing information compared to the RLD.[6]

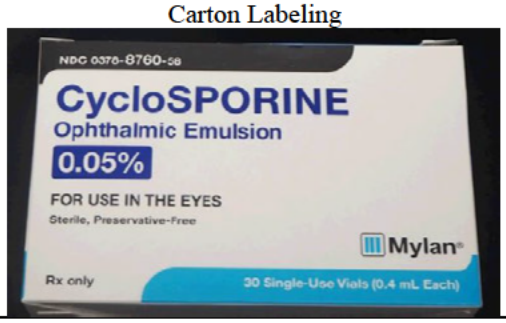
Table 3: Labeling Comparison: RLD vs. Proposed Generic Product

Delivery Device-Related Labeling*	**Yes/No/NA**
(1) Any difference in the **Dosage and Administration (Section 2 of PI)**?	**No**
(2) Any difference in the **Dosage Forms and Strengths (Section 3 of PI)**?	**No**
(3) Any difference in the **How Supplied/Storage and Handling (Section 16 of PI)**?	**Yes**
(4) Any differences in the **IFU (if available)**?	**N/A**
(5) Any differences in the **packaging (e.g., carton, container) labeling (if applicable)**?	**Yes**

* does not include differences in labeling due to use of non-propietary name; N/A=not applicable

The following table presents side-by-side comparison of the labeling differences.

Table 4: Comparison of Selected Portions of Labeling

RLD (NDC 050790)	**Proposed (ANDA 205894)**
Carton Labeling 	Carton Labeling 
Secondary Packaging Label Not applicable	Secondary Packaging Label 

[6] \\CDSESUB1\evsprod\anda205894\0055\m5\53-clin-stud-rep\535-rep-effic-safety-stud\increase-tear-production\5354-other-stud-rep\gdd-doc-2021-0890\gdd-doc-2021-0890-study-report.pdf

RLD (NDA 050790)	Proposed (ANDA 205894)
Excerpt of RLD Prescribing Information[7]	Excerpt of Proposed Prescribing Information[8]
"16 HOW SUPPLIED/STORAGE AND HANDLING RESTASIS® ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 30 or 60 vials are packaged in a polypropylene tray with an aluminum peelable lid. The entire contents of each tray (30 vials or 60 vials) must be dispensed intact."	"16 HOW SUPPLIED/STORAGE AND HANDLING Cyclosporine ophthalmic emulsion, 0.05% is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.5 mL natural colored low density polyethylene vial; five vials are packaged in an aluminum pouch and six pouches are packaged in a carton. The entire contents of each carton (30 vials) must be dispensed intact. Cyclosporine ophthalmic emulsion is also provided in a 60 count carton that must be dispensed intact.""

Source: Adapted from Response to Information Request received on November 5, 2021, RLD prescribing information approved on July 18, 2017, and proposed prescribing information submitted to ANDA 205894 on January 20, 2022

Reviewer Comments:
The main differences in labeling are related to the carton and secondary packaging. These differences are primarily due to the differences in packaging design, and the language accurately describes the proposed product's packaging. These are minor differences.

3 CONCLUSION

From a clinical safety perspective, there are only minor design differences between the RLD and proposed drug product. Therefore, DCR concludes this generic product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic product, and that the differences as compared to the RLD do not alter the clinical effect or safety profile of this proposed ANDA product under the conditions of use as specified in the labeling. In summary, DCR finds the proposed drug delivery device user interface for the proposed generic product acceptable.

4 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative (threshold) analyses and has no recommendations/the following deficiencies:

☐ Major
☐ Minor
☒ N/A (Review is Adequate)

[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050790s027lbl.pdf
[8] \\CDSESUB1\evsprod\anda205894\0056\m1\us\114-labeling\final\package\final-package-insert.pdf

William Chong

Digitally signed by William Chong
Date: 1/28/2022 02:09:36PM
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OPMA Report for Consult Request from OLDP on ANDA#205894

Purpose:

To illustrate the viewpoint and assessment from OPMA on the drug product manufacturing process (b) (4) in the generic drug application, ANDA#205894 Cyclosporine ophthalmic emulsion 0.05% from Mylan Pharmaceuticals Inc.

Background:

(b) (4)

(b) (4)

Yaodong Huang

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Mahesh Ramanadham

Digitally signed by Mahesh Ramanadham
Date: 4/22/2020 02:30:35PM
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Office of Generic Drugs
DQMM/ORS/OGD CONSULT REVIEW

To:	Nilufer M. Tampal, Ph.D. Director Division of Bioequivalence III (DBIII) Office of Bioequivalence (OB) OGD
RE:	**ANDA 205894**
Consult No:	Not Available
Consult Date:	August 10, 2017
Drug Product:	Cyclosporine Ophthalmic Emulsion 0.05%
Sponsor:	Mylan Pharmaceuticals
Date of Review:	08/17/2017
Reviewer:	Meng Hu, Ph.D., Science Reviewer, DQMM/ORS/OGD
Through:	Liang Zhao, Ph.D., Director, DQMM/ORS/OGD

Reason for Consultation

On August 10, 2017, DBIII sent a consult to ORS/DQMM regarding ANDA 205894 for the generic drug product for Cyclosporine Ophthalmic Emulsion, 0.05%, sponsored by Mylan Pharmaceuticals. Specifically, DBIII has the following questions/requests for DQMM:

A. Please conduct and provide the results of the following analyses for the GSD study (1 in 100 dilution) submitted in the current amendment dated 07/06/2017 (module 5.3.1.2): 1) Earth Mover Distance (EMD) analysis from the tabulated histogram raw data to assess profile similarity between the test and reference products, and 2) population bioequivalence (PBE) analysis on the EMD results.

B. Please comment on the appropriateness of the EMD and statistical analysis approach used by the firm to assess bioequivalence for the GSD data in Report No. CPS-PBE-Attachment-4 (amendment dated 02/08/2017, module 1.12.15).

Note: In the amendment dated 07/06/2017, the firm submitted SAS transport files to assess the difference (in terms of distance) between the shapes of globule size distribution (GSD) profiles for each of the 3 lots of the test (Nos. 01813A, 01813B, 03912A) and RLD (Nos. 80773, 80796, 81028) products. GSD data was submitted for 100X diluted samples. The firm used dynamic light scattering (DLS) to generate GSD data using narrow mode (Report No. CPS-PBE-Attachment-4, amendment dated 02/08/2017, module 1.12.15).

EXECUTIVE SUMMARY

DQMM Review Summary:

Per current guidance on Cyclosporine emulsion[1], DQMM's conducted bioequivalence analysis based on the Firm's GSD data measured by DLS for 100X diluted samples of the test and reference-listed drug (RLD) products. Table 1 and 2 show the results of EMD and PBE analysis, respectively. The results indicate that the sponsor's product **is equivalent** to the RLD product (i.e., Restasis) based on profile comparison of GSD.

Of note, DQMM does not agree with the sponsor's EMD analysis. The firm's implementation of EMD algorithm is not consistent with the referred publication in current guidance for EMD method[2]. Besides, in the report (Report No. CPS-PBE-Attachment-4, amendment dated 02/08/2017), the firm did not provide any other reference for their implementation of EMD method either.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf

[2] Yossi Rubner, Carlo Tomasi and Leonidas J. Guibas. The earth mover's distance as a metric for image retrieval. International Journal of Computer Vision, 40(2):99-121, 2000.

EMD-based statistical analysis for equivalence testing of particle size distribution for cyclosporine emulsion

DLS data

Sponsor provided the intensity-weighted histogram data of GSD as determined by the DLS method for both the RLD and test products. Note that the testing was conducted on3 lots each of the RLD product and the proposed product, for which 30 samples (10 vials X 3 aliquots) were collected from each lot and each sample was tested 3 times (i.e., 3 replicates) each at the 1:100 dilutions.

Fig. 1 shows the DLS profiles from RLD samples (thin blue), as well as the grand average profile (bold red) with 1:100 dilutions. The GSD profile of each sample is represented by the average of 3 replicates. From the DLS profile, we can clearly see the multi-modal (i.e., multiple peaks) pattern in GSD of the cyclosporine emulsion, which calls for a suitable method for profile analysis such as the EMD method.

Figure1. Globule size distributions (GSDs) for the RLD. In the figure, blue lines refer to individual RLD samples, whereas red line corresponds to RLD mean profile (i.e., the RLD center)

Rationale for the EMD approach

To demonstrate bioequivalence based on particle size distribution profiles, the conventional D50/SPAN is the most frequently used method, where D50 reflects the 50th percentile of the distribution (or median) and SPAN refers to the difference between the 90th and 10th percentiles divided by the 50th percentile. In spite of its popularity for demonstrating bioequivalence, this method essentially evaluates specific portions of the size profile and assumes the monomodal pattern in particle size distribution [3]. Therefore, the D50/SPAN is inadequate for our purpose as the GSD for the RLD is not monomodal.

The analysis of non-monomodal size distribution usually requires the whole profile assessment. Previously, a modified chi-square ratio statistic was proposed for the whole profile analysis to demonstrate bioequivalence of orally inhaled drug products [4]. Note that this method (and all other Chi-square based methods) can only be utilized to analyze data whose average profile does not contain zero values, as the average profile is used as denominator in the calculation. Although this is usually not an issue for orally inhaled drug products using the multi-stage cascade impactors for particle size determinations, the chi-square method is inappropriate for GSD data by DLS as it is common to observe "zero" values in the average GSD profile.

We applied a statistical bioequivalence approach based on a whole profile analysis, which does not assume any particular pattern of particle size distribution. Specifically, the method suggested in the PSG, i.e., the earth mover's distance method (EMD) [5-6], is a widely-used statistical metric for assessing the differences between two distributions (or histograms) [7-9] that utilizes data over the whole size distribution profiles, which is then subjected to a population bioequivalence testing (PBE) [10], a comprehensive bioequivalence statistical method taking into account both mean and variance information. Given the features of EMD method and PBE, this approach can provide a rational methodology for establishing equivalence of multi-modal particle size distributions between test and reference products.

The Methodology: EMD computation followed by PBE analysis

We applied the EMD-based approach followed by PBE analysis to compare multi-modal particle size distributions to: (1) reduce the dimension of data by calculating the distance between profiles, thus bypassing the multivariate comparisons and (2) perform the bioequivalence test of the above calculated distances using a PBE analysis method that compares both the mean and variance of 'Reference' and 'Test' drug products [12]. Please refer to references [6, 12] for the detailed descriptions for these two methods. Fig. 2 illustrates the approach that includes the following steps:

1. Given 2 sets of profiles (Reference vs. Test), a ‘Reference center’ is first computed by taking the grand average of all Reference profile data.

2. The EMD is applied to calculate the distance between the ‘Reference center’ and the individual Reference profile, shown as [ ] (where *i*, *j*, *k* refer to the index of ‘Lot’, ‘Sample’, ‘Replicate’, respectively), to represent the deviation between the individual Reference sample and Reference center. In the same manner, the EMD is then employed to calculate the distance between the ‘Reference center’ and the individual Test profile, which is given as [ ] (where *i*, *j*, *k* refer to the index of ‘Lot’, ‘Sample’, ‘Replicate’, respectively), to represent the deviations of the individual Test sample from the Reference center.

3. PBE is applied as the statistical test between two groups (Test and Reference) of distances to establish the equivalence for the Test and Reference product. BE is concluded if the ‘Test’-‘RLD center’ distances have the comparable mean and variance with the ‘RLD’-‘RLD center’ distance; i.e., the linearized criteria (95% confidence upper bound) is not greater than zero [1].

The established EMD-based approach essentially analyzes the difference between Test and Reference and the difference within Reference, which is an approach to equivalence testing without assumptions. We also take advantage of PBE in dealing with datasets that contain multi-level structure (i.e., ‘Lot’ x ‘Sample’ x ‘Replicate’) as the calculated EMD distances can be directly compared in the PBE analysis without losing the data structure information.

Figure 2. Schematic diagram of the EMD/PBE approach

Application to Mylan DLS data

RLD-Test profile comparison

Fig. 3 (a) shows the GSD profiles from individual samples of RLD and Test products. Fig. 3 (b) shows the mean (±SD) profiles of RLD and Test products. It is observed that the GSD profiles of the test and RLD products have difference in the joint area between two peaks (around 58.8 nm), but the test product still exhibits the bimodal pattern (i.e., the small peak before 58.8 nm overlaps on the left shoulder of large peak after 58.8 nm).

(a) (b)

Fig.3. Visual inspection of RLD and Mylan samples. Panel (a) shows the DLS profiles from individual samples of RLD (blue) and Test (red). Panel (b) shows the mean (±SD) profiles of the Myaln (red) and Reference product (blue), where the mean profiles (bold curve) are flanked by the dotted SD curves.

The EMD-based approach was then applied to compare GSD profiles of RLD and test product. Fig. 4 shows the distributions (by boxplot) of calculated EMD distances between the individual RLD profile and RLD center (right boxplot) and the distances between the individual Mylan profile and RLD center (left boxplot). The means and variances of two groups of distances are presented in Table 1. Subsequently, the PBE method is applied to the two groups of the calculated EMD distances to evaluate if they have comparable means and variabilities for the BE conclusion. The results of PBE analysis are shown in Table 2. As the linearized criterion (95% confidence upper bound) was calculated to be -0.3771 (less than zero [1]), the test product is concluded equivalent to the RLD product based on profile comparison of GSD.

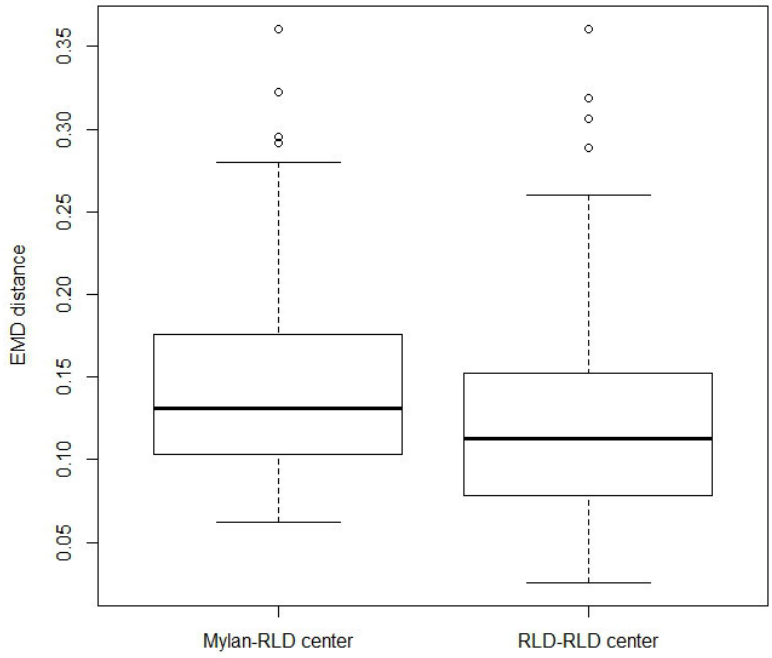

Fig. 4. The calculated EMD distances of Reference (right) and the Mylan profiles (left) to the Reference center, respectively. See Table. 1 for the means and variances of these two groups of EMD distances.

Table. 1. Means and variances of two groups of distances (i.e., R-R vs. T-R) (same data with Fig. 4)

Distance	Mean	Variance
Test - RLD center	0.1435	0.0029
RLD - RLD center	0.1199	0.0029

Table 2. PBE analysis based on calculated EMD distances for the test and RLD products

Variable	Sigma_R	Scaled	Linearized Point Estimate	95% Upper Confidence Bound	PBE Result
EMD	0.4562	Reference	-0.4644	-0.3771	PASS

References

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf

[2] Ziyaur Rahman, Xiaoming Xu, Usha Katragadda, Yellela S. R. Krishnaiah, Lawrence Yu and Mansoor A. Khan, Quality by design approach for understanding the critical quality attributes of cyclosporine ophthalmic emulsion. Molecular Pharmaceutics, 11, 787−799, 2014.
[3] Dynamic light scattering common terms defined. Inform White Paper, Malvern Instruments Limited, 2011. http://www.biophysics.bioc.cam.ac.uk/wp-content/uploads/2011/02/DLS_Terms_defined_Malvern.pdf
[4] Benjamin Weber, Sau L. Lee, Renishkumar Delvadia, Robert Lionberger, Bing V. Li, Yi Tsong and Guenther Hochhaus. Application of the modified chi-square ratio statistic in a stepwise procedure for cascade impactor equivalence testing. AAPS Journal, 17(2), 370-379, 2015.
[5] Shmuel Peleg, Michael Werman, and Hillel Rom, A unified approach to the change of resolution: Space and gray-level. IEEE Transactions on Pattern Analysis and Machine Intelligence, 11:739–742, 1989.
[6] Yossi Rubner, Carlo Tomasi and Leonidas J. Guibas, The earth mover's distance as a metric for image retrieval. International Journal of Computer Vision. 40(2), 99–121, 2000.
[7] Kangyu Ni, Xavier Bresson, Tony Chan and Selim Esedoglu, Local histogram based segmentation using the wasserstein distance. International Journal of Computer Vision, 84: 97–111, 2009
[8] Haibin Ling and Kazunori Okada, An efficient earth mover's distance algorithm for robust histogram comparison. IEEE Transactions on Pattern Analysis and Machine Intelligence, 29(5), 840-53, 2007.
[9] Darya Y. Orlova, Noah Zimmerman, Stephen Meehan, Connor Meehan, Jeffrey Waters, Eliver E. B. Ghosn, Alexander Filatenkov, Gleb A. Kolyagin, Yael Gernez, Shanel Tsuda, Wayne Moore, Richard B. Moss, Leonore A. Herzenberg and Guenther Walther, Earth mover's distance (EMD): a true metric for comparing biomarker expression levels in cell populations. PLoS ONE, 11(3): e0151859, 2016.
[10] Guidance for Industry - Statistical Approaches to Establishing Bioequivalence, 2001. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf
[11] Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm, 15(6), 657-80, 1987.
[12] Robert Schall and Herman G. Luus. On population and individual bioequivalence. Statistics in medicine, 12, 1109-1124, 1993.

Office of Generic Drugs
DQMM/ORS/OGD CONSULT REVIEW

To:	Nilufer M. Tampal, Ph.D.
Re:	ANDA 205894
Consult No:	Not Available
Drug Product:	Cyclosporine Ophthalmic Emulsion 0.05%
Sponsor:	Mylan Pharmaceuticals
Date of Review:	06/28/2016
Reviewer:	Meng Hu, Ph.D. (DQMM/ORS/OGD) Stephanie Choi, Ph.D. (DTP/ORS/OGD) Xinyuan (Susie) Zhang, Ph.D. (DQMM/ORS/OGD)

Statistical analysis on globule size distribution (GSD) of cyclosporine ophthalmic emulsion using Earth Mover's Distance (EMD) and Population Bioequivalence (PBE) methods

Executive Summary

The GSD of test and reference products were determined by the Division of Product Quality Research (DPQR) lab using ANDA samples submitted by the sponsor (from 3 exhibit lots) and multiple lots of Restasis (the reference listed drug or the RLD). DPQR measured the GSD using both dynamic light scattering (DLS) and laser diffraction (LD).

Statistical evaluation of GSD was performed using both PBE on the entire profile and EMD. The EMD methodology was described under the Bioequivalence Primary Review task in ANDA 203880. Results indicate that Mylan's product is inequivalent to Restasis in terms of the GSD profile when analyzed by both PBE and EMD methods on both DLS and LD data.

Analysis on DLS data

Data

DPQR tested RLD and Mylan products by DLS, in which RLD had 9 lots and Mylan had 3 lots, and 3 samples were tested for each lot with 6 replicates (only first 3 were used to take into account both within and between sample variability). Fig. 1 (a) shows the profile from individual samples presented as the mean of the first three measurements of RLD and Test. Fig. 1 (b) shows the mean (bold) and standard deviation (dashed) of RLD and Test. We observe that both the RLD and the Mylan products reproduce a little bump (around 50 nm) in their individual profiles. However, the Mylan product exhibits slightly shifted right peak, compared to RLD profile.

(a) (b)

Figure 1. Visual inspection of RLD and Mylan samples.

Mylan vs. RLD

We have 27 (9 lots X 3 samples) RLD samples and 9 (3 lots X 3 samples) Mylan samples, and used first 3 measurements for each sample. In a typical test, we randomly select 9 RLD samples, and then applied proposed EMD approach to estimate the confidence interval (upper limit) of (T-R)/(R-R). We then repeat the random selection 200 times. Fig. 2 shows the typical grand average of RLD and Mylan profiles (over all lots, samples and replicates). Fig. 3 shows the distributions of T-R and R-R distances by EMD.

Figure 2. A typical observation for sample average of RLD and Mylan

Figure 3. Distribution of T-R and R-R distances by EMD using data in Fig. 2.

For this ANDA, the proposed EMD approach finally gives a 95% confidence interval of (T-R)/(R-R) as [102% ~ 115%]. After 200 random selections, all upper limits of RLD vs. Mylan are shown in Fig. 4 (right boxplot). The left boxplot shows all the upper limits of RLD vs. RLD comparison (i.e., using RLD sample as the Test sample). If the 90% quantile **(113.79%)** of the upper limits of RLD vs. RLD comparison is considered as a threshold (i.e., by this threshold, the RLD product has the passing rate of 90% comparing to itself), the test sample has the passing rate of 56.5% over 200 random selections. The criteria is yet finally determined. The current thinking is that the passing rate of Test sample should be comparable with 90%, e.g., at least 80%.

Figure 4. Upper limits of RLD vs. Myaln (right boxplot) and RLD vs. RLD (left boxplot) by the EMD approach.

Summary from analysis of DLS data

The EMD analysis results suggest that the Mylan product is **inequivalent to the RLD product** in terms of the GSD.

Analysis on LD data

Data

DPQR tested RLD and Mylan products by LD, in which RLD and Mylan had 3 lots respectively, and 3 samples were tested for each lot with 6 replicates (measurements). Fig. 5 (a) shows the profile from individual samples of RLD and Test. Fig. 5 (b) shows the mean (bold) and standard deviation (dashed) of RLD and Test.

(a) (b)

Figure 5. Visual inspection of RLD and Mylan samples by LD.

From visual inspection, we can see that there is a significant difference between the test and RLD samples.

Mylan vs. RLD

We have 9 (3 lots X 3 samples) RLD samples and 9 Mylan samples, and use first 3 measurements for each sample. Unlike the DLS data, the LD data do not apply the random selection due to the limited number of RLD samples. We applied proposed EMD approach to estimate the 95% confidence interval (upper limit) of (T-R)/(R-R). The proposed EMD-based approach yields the upper limit of (T-R)/(R-R) as 558%, which indicates that the Test is not equivalent to RLD. We don't have enough LD data to calculate the threshold as indicated in the DLS results. But referring to the threshold from DLS (i.e., **113.79%**), the 558% is far greater than that (almost 5-fold).

Summary from analysis of LD data

1. Preliminary results by EMD suggest that the Mylan product is highly likely **inequivalent to the RLD product** in terms of LD data. However, the LD data from additional RLD lots are needed to confirm the results for LD (only 3 lots of RLD are used in the current analysis, whereas 9 lots of RLD were used in the DLS analysis to establish the variability of the RLD). DPQR is currently measuring additional RLD lots using LD for ORS to validate this method for LD.

Appendix

PBE test was applied to D50 and SPAN for DLS and LD data of the Mylan product measured by DPQR.

PBE analysis on DLS data

Since we have more than 3 lots RLD data (each lot having 3 samples), 9 RLD samples (each with first 3 measurements) were randomly selected to compare with the Mylan samples (each with first 3 measurements) for each test (narrow mode, 10x dilution). The test was then repeated 200 times. The PBE results show that the Mylan data has 0.5% and 98.5% passing rate with D50 and SPAN in log-scale, respectively. Table 1-2 show the typical PBE test results for D50 and SPAN, respectively.

Table 1. *PBE for D50 (log-scale)*

σ_{T0}	σ_R	Scale	Point estimate of criteria	Upper limit of criteria	PASS or FAIL
0.1	0.114	Reference	-0.016	0.009	FAIL

Table 2. *PBE for SPAN (log-scale)*

σ_{T0}	σ_R	Scale	Point estimate of criteria	Upper limit of criteria	PASS or FAIL
0.1	0.383	Reference	-0.332	-0.156	PASS

PBE analysis on LD data

PBE is applied to RLD and Mylan LD data (narrow mode, 4→300 dilution). Table 3 and Table 4 show the PBE test results for D50 and SPAN, respectively.

Table 3. *PBE for D50 (log-scale)*

σ_{T0}	σ_R	Scale	Point estimate of criteria	Upper limit of criteria	PASS or FAIL
0.1	0.037	Constant	-0.005	0.001	FAIL

Table 4. *PBE for SPAN (log-scale)*

σ_{T0}	σ_R	Scale	Point estimate of criteria	Upper limit of criteria	PASS or FAIL
0.1	0.033	Constant	0.058	0.070	FAIL

Summary from PBE analysis of DLS and LD data

Results from the PBE analysis conducted on the entire globule size distribution for both DLS and LD suggest that the Mylan product is **inequivalent to the RLD product** in D50 and SPAN.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205894Orig1sS000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL AP or TA (NEW STRENGTH)**

RPM and TL: Daniil Marchuk & David Eng

ANDA #: 205894 Applicant: Mylan Pharmaceuticals Inc.
Established Product Name: Cyclosporine Ophthalmic Emulsion, 0.05%

Basis of Submission (BOS)/RLD (Application#/Proprietary Name/Applicant): NDA 50790 / Restasis Ophthalmic Emulsion, 0.05% / Allergan, Inc.

If BOS discontinued: [insert hyperlink to FRN] ☐ Safety/effectiveness FRN pending

Select, as applicable:

☒ RX ☐ OTC

☐ History of tentative or split approval action

☐ Shared Bio Studies (list ANDA number(s)) ☐ Shared Labeling (list ANDA number(s) _____)

☒ Memo uploaded for PAL item or OGDP confirmation

Priority: ☒ First Generic Approval (i.e., no other generics approved) ☐ Drug Shortage ☐ PEPFAR ☐ CGT

☐ Other priority _____

Misc: ☐ REMS ☒ Combination product ☐ Suitability Petition ☐ 180-day language ☐ MOU ☐ PEPFAR

☒ ***RPM Has Verified the Following:*** **Date: 1/30/2022**

1. ANDA number, NDA/RLD, Drug product and strength(s) are correct on all discipline/subdiscipline reviews
2. All submissions have been reviewed: Relevant disciplines are adequate and finalized/archived in the appropriate system of record
3. Most recent BE guidance is included in the review or a memo has been uploaded
4. No RLD updates or changes to exclusivity/patents impact endorsed labeling
5. All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d). (Not applicable to supplements)
6. OSIS Clinical Endpoint and Bioequivalence Site Inspections acceptable or not applicable
7. No blocking legal or regulatory issue (refer to Policy Alert Tracker)
8. OGD Communications has been notified if Priority Approval (First generic, Drug Shortage, PEPFAR, CGT, other OGD Communications priorities)
9. OMIR is Approve with no new facility alerts and a DP and API manufacturer listed in Submission Facility Status View
10. No open issues or tasks in Platform
11. No pending consults
12. Filing review completed for NSA or reformulation
13. PNR review is current
14. Correct language, format and content in action letter (e.g., relevant contact from 356h form)
15. Endorsements are within 29 days

Discipline Completion Dates:

Bioequivalence **1/31/2022** Labeling **1/28/2022** Clinical **N/A**	Integrated Quality Assessment: **N/A** If there is no IQA, provide the applicable date(s): • Chemistry **2/1/2022** • Microbiology **1/31/2022** • Biopharmaceutics/Dissolution **N/A** DMF No(s). (b) (4) Date(s) Acceptable **1/19/2022**

Additional Notes (if applicable)

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 1/31/2022
Name: RTP

Patent/Exclusivity Certification:

☐ **No Relevant Patents** ☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** ☐ **section viii**

Reminders:
- Check the policy alert list for any pending exclusivity determinations
- Verify in the Orange Book there are no unexpired ODE's that cover the active moiety
- Confirm the ANDA is not blocked by other ANDA's eligibility for 180-day CGT exclusivity
- Confirm S/E determination completed for RLDs in the discontinued section of the OB

RLD = Restasis NDA# 50790 ☒ **RX or** ☐ **OTC**
Date Checked in Orange Book#: 1/27/2022

Type of Letter:
☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL AP or TA (NEW STRENGTH)

Forfeiture Information
- Confirm whether the first applicant remains eligible for 180-day exclusivity (i.e., that a forfeiture event under section 505(j)(5)(D) has not occurred) and document the determination

Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐
If yes, the date forfeiture memo was completed
Date _____ ANDA # _____

Competitive Generic Therapy 75 Day Special Forfeiture Rule:
First Applicant: ANDA # _____
Date of Approval: _____
75 Day Date: _____

180 Day Exclusivity Information
Is applicant eligible for H-W 180 day exclusivity Yes ☐ No ☒
☐ Sole
☐ Shared
Is applicant eligible for CGT 180 day exclusivity Yes ☐ No ☒
☐ Sole
☐ Shared
Is applicant blocked by a triggered CGT 180 day exclusivity
Yes ☐ No ☐
If no, the date and time checked for notification of commercial marketing: Date _____ Time: _____

Comments: BOS: 50790M Restasis single use vials. ANDA submitted on 11/1/2013 with PIII certification to '979 patent (expired on 5/17/2014). ACK for filing on 11/1/2013 (LO date 7/17/2015).
Patent amendment rec'd on 1/15/2014 (pre-filing): PIV certification to the '111 patent (later-listed).
Patent amendment rec'd on 1/16/2014 (pre-filing): PIV certification to the '111 patent (later-listed). Mylan submitted the exact same file, dated January 14, 2014, on January 15, 2014, in response to center acknowledgement.
Patent amendment rec'd on 1/23/2014 (pre-filing): PIV certification to the '162 patent (expires 8/27/2024), associated with U-1479 (later-listed).
Patent amendment rec'd on 2/06/2014 (pre-filing): PIV certification to the 8,652,556 patent (not listed in OB).
Patent amendment rec'd on 2/18/2014 (pre-filing): PIV certification to the '048 patent (expires 8/27/2024) associated with U-1483 (later-listed).
Patent amendment rec'd on 2/28/2014 (pre-filing): Corrected the typographical error contained to the patent number cited in their 2/6 amendment. PIV certification to the 8,642,556 patent (expires 8/27/2024) (later-listed).
Patent amendment rec'd on 4/3/2014 (pre-filing): PIV certification to the '930 patent (later-listed).

General correspondence rec'd on 7/22/2014 (pre-filing): Copy of July 21, 2014 letter, Mylan, through counsel (Hunton and Williams), asked the FDA to "confirm" the patent amendment (related to the '111 patent) had been submitted on January 14, 2014, for purposes of establishing first applicant eligibility. In support of this argument, Mylan submitted evidence purporting to show that it had transmitted a complete patent amendment.
General correspondence rec'd on 12/31/2014 (pre-filing): Copy of December 22, 2014 letter, Mylan, through counsel to "confirm" the patent amendment had been submitted on January 14, 2014.
General correspondence rec'd on 3/18/2015: Copy of March 17, 2015 letter, Mylan, through counsel Mylan provides its record of the patent amendment's actual transmission to the Gateway (this is following FDA's request, sent via email dated January 9, 2015). Among other things, Mylan's letter again referred to the January 14, 2014 message delivery notification and center acknowledgement.
Patent amendment rec'd on 7/20/2015: Notification that Mylan has provided notice to the owners of the patent and NDA holder and commitment to amend the ANDA to provide documentation that notice was received.
FDA issued a response to Hunton and Williams on 7/20/2015: The letter was in response to Mylan's letters dated July 21, 2014 and March 17, 2015 requesting confirmation of patent amendment (related to the '111 patent) to have been submitted on 1/14/2014. FDA concludes the correct submission date for Mylan's patent amendment to ANDA 205894 is January 15, 2014.
Patent amendment rec'd on 7/22/2015: In accordance with 21 CFR 314.95(e), amendment provides documentation of receipt of the notice. Proof of delivery by (b) (4) evidences receipt by Allergan, Inc. in Irvine, CA signed and delivered on July 21, 2015.
On 7/27/2015, FDA issues a Dear Applicant letter (via email) [Cyclosporine Docket 2014-N-0087] to solicit comments on 180 day exclusivity matters related to Cyclosporine Ophthalmic Emulsion, 0.05%. The particular issues that are subject to the letter are 1) whether or one more applicants that submitted a paragraph IV certification to the '979 before January 14, 2014 but was not received for review until after the patent expired qualifies as "first applicant" and 2) whether a forfeiture event under 505(j)(5)(D)(i)(VI) of the FD&C Act has occurred.
On 7/28/2015, FDA issues a revised Dear Applicant letter (via email). The letter is identical to the July 27, 2015, with the exception to citing a new docket number, 2015-N-2713.
General correspondence rec'd on 7/28/2015: In response to FDA's July 20, 2015 letter, Mylan requests FDA to reconsider our July 20, 2015 decision and provides additional evidence/arguments.
General correspondence rec'd on 8/19/2015 and 8/27/2015: copies of correspondence sent to OGDP on August 18, 2015 by Hunton and Williams asking FDA to make a final determination with respect to the date on which Mylan submitted a complete patent amendment. In response to an FDA email dated August 17, 2015, Mylan submits additional supporting documentation.
Paper jacket rec'd on 8/27/2015: Correspondence from Fish & Richardson stating a civil action for patent infringement had been filed 8/24/2015 in USDC of Texas on the '111, '162, '556, '048 and '930 patents.
Patent amendment rec'd on 9/11/2015: On August 24, 2015, suit filed by Allergan with respect to the '111, '162, '556, '048, '930 patents in the USDC for the Eastern District of Texas (civil action no 2:15-cv-01455). A copy of compliant was provided. [Note, these patents were not listed at the time of original submission '111, '162, '556, '048, and '930 patents, therefore these patents do not give rise to a statutory 30-month stay of approval of this ANDA.]
FDA issued a response to Hunton and Williams on 9/18/2015: The letter was in response to Mylan's letters dated July 27, 2015 and August 18, 2015. FDA reaffirms its conclusion that the patent amendment containing a PIV certification regarding the '111 patent is January 15, 2014.
Patent amendment rec'd on 3/18/2016: PIV to newly listed '191 patent associated with use code U-1479.
Patent amendment rec'd on 4/14/2016: In accordance with 21 CFR 314.95(e), amendment provides documentation of receipt of the notice. Proof of delivery by (b) (4) evidences receipt by Allergan, Inc. in Parsippany, NJ signed and delivered on March 21, 2016.
Patent amendment rec'd on 5/10/2016: On February 18, 2016, an amended complaint for patent infringement of the '191 patent was filed Allergan in the USDC for the Eastern District of Texas (civil action no 2:15-cv-01455). A copy of compliant was provided. [Note, the '191 patent was not listed at the time of original submission, therefore this patent does not give rise to a statutory 30-month stay of approval of this ANDA.]
Patent amendment rec'd on 9/13/2018: On October 16, 2017, the USDC for the Eastern District of Texas entered a Final Judgment in favor of Mylan that the asserted claims 26-27 of the '111 patent; claims 1, 11, 13, 14 and 23 of '048 patent; claim 35 of the '930 patent; and claims 13, 16, 22, 26 and 27 of the '191 patent are declared invalid on the ground of obviousness. In

the Findings of Fact in support of its Final Judgment, the USDC for the Eastern District of Texas noted (at page 29) that Allergan dropped the assertion of and gave Mylan a covenant not to sue with respect to '162 and '556 prior to trial. Copies of the final judgment and findings of fact provided. Mylan also informs FDA that on October 27, 2017, Allergan appealed the Final Judgment of invalidity entered by the USDC for the Eastern District of Texas to the CAFC (case 2018-1130) and that appeal is pending. Notice of appeal was not provided.
Patent amendment rec'd on 11/26/2018: On November 13, 2018, the CAFC affirmed the Eastern District of Texas court's Final Judgment. A copy of the Federal Circuit's judgment provided.
Patent amendment rec'd on 12/17/2020: Reformulation amendment to be Q1/Q2 the same as the RLD product, addressed 314.96(d)(1) by providing new PIV certifications to '111; '162, '556, '048, '930, and '191 patents.
Patent amendment rec'd on 1/15/2021: In accordance with 21 CFR 314.95(e), Mylan provides (b) (4) receipts to document receipt of notice by Allergan, Inc., and Saint Regis Mohawk Tribe, both signed and delivered on 12/18/2020.
Patent amendment rec'd on 2/10/2021: Mylan informs that no suit was filed within the noted 45-day period.

Application is eligible for final approval as all claims to 180 day have extinguished.

180 Day/CGT Exclusivity Status/Landscape: Under the FDA's interpretation of "first applicant", Innopharma was a first applicant but since the '979 patent expired results in a forfeiture event under section 505(j)(5)(D)(i)(VI). Alterntatively, neither Teva (b) (4) has marketed its drug products under ANDA 203880 (b) (4), respectively, by May 27, 2019. Therefore, even if Teva and Akorn were regarded as a "first applicant," both have forfeited their eligibility for 180-day exclusivity under the failure to market provision at section 505(j)(5)(D)(i)(i) of the FD&C Act. See Dear Applicant letter for complete details.
If known, impact on pending exclusivity determinations: none
If Tentative Approval, if known, anticipated full approval date:

2. Final Decision

Date: 2/2/2022
Name: ATP

☒ Verified the following:

1. Completion of the following endorsement tasks, if applicable:
   - **a. Division of Legal and Regulatory Support Endorsement**
   - **b. Paragraph IV Evaluation**
   - c. REMS Endorsement
   - **d. Quality Endorsement**
   - **e. Bioequivalence Endorsement**
   - f. Clinical-Bioequivalence Endorsement
   - **g. Labeling Endorsement**
   - **h. RPM Team Leader Endorsement**
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates in DARRTS since the Labeling Endorsement
5. No new issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments received since Quality Endorsement
9. No new amendments received since the RPM Team Leader Endorsement

This **ANDA** is ready for **FULL APPROVAL**.

****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL****

(b) (4)

(b) (4)

(b) (4)

[redacted]

Endorsement Signatures (To be provided by endorsees in the event of Platform unavailability):

- Division of Legal and Regulatory Support Endorsement
  - Sign & Date_____
- Paragraph IV Evaluation
  - Sign & Date_____
- REMS Endorsement
  - Sign & Date_____
- Quality Endorsement
  - Sign & Date_____
- Bioequivalence Endorsement
  - Sign & Date_____
- Clinical-Bioequivalence Endorsement
  - Sign & Date_____
- Labeling Endorsement
  - Sign & Date_____
- RPM Team Leader Endorsement
  - Sign & Date_____
- ORO IO Endorsement
  - Sign & Date_____

REFERENCES / ASSOCIATED DOCUMENTS

Reference Name
4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Author	Role	Version	Change Date	Summary of Changes
Heather Strandberg	Author	1.0	2014-10-01	New Form
Kevin Denny	Reviser	2.0	2017-10-03	Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 Remove content adequately captured in the platform Update information captured in the Division of Legal and Regulatory Support Endorsement section Other minor administrative corrections to format and content
Kevin Denny	Reviser	3.0	2018-01-14	Update Final Decision section
Joe Shin	Reviser	4.0	2019-03-04	Changes made: 1) "No Relevant Patents" checkbox added to patent types; 2) Basis of Submission was updated to include (NDA#/Proprietary Name/Applicant); 3) Removed "(CR)" from the second checkbox in the RPM Evaluation section; 4) Added "Shared BE studies..." and "Shared Labeling..." bullets to the review date section; 5) Added a not applicable checkbox for the MMA question; 6) Sentence revised to include not applicable cases in the OSIS question
John Ibrahim/QM Team	Reviser/QM	5.0	2021-08-18	• Update page 1 (revisted ANDA information section, RPM checklist, and discipline completion dates) • QM Team updated Header, document #, & title to conform to OGD Controlled Documents Program naming conventions & formatting standards • QM Team updated Footer to conform to ISO 8601 – International Time & Date Standards

Memorandum to File – Addendum to Microbiology Review

To: **Abbreviated New Drug Application (ANDA) 205894 from Mylan Pharmaceuticals Inc. for Cyclosporine Ophthalmic Emulsion 0.05%**

From: CAPT Paul Dexter
CDER/OPQ/OPMA/DMAI/MAB1

Dr. Elizabeth Bearr
CDER/OPQ/OPMA/DMAI/MAB1

Date: **January 31, 2022**

Subject: Addendum to Microbiology Review Completed on August 2, 2021 for ANDA 205894

The purpose of this Addendum is to revise and clarify certain statements in the Microbiology Review (hereinafter referred to as the review) for ANDA 205894 completed by CAPT Paul Dexter and Dr. Elizabeth Bearr on August 2, 2021 and added to Panorama on August 6, 2021.

The review was written to document an assessment of whether a formulation change raised any new product microbiology concerns. After the review was completed, certain statements were identified that warranted correction.

These include the following:

1. In the table on page 1 listing submissions being reviewed, the first row indicates a submission submitted on 12/17/2020 and received on 12/17/2019. Both dates should be 12/17/2020.
2. (b) (4)

In addition, this addendum clarifies that while the two rows in the submission history which are identified as relating to Microbiology Review #3 indicate reviews from 10/15/2018 and 11/1/2018, both submissions are discussed in a single microbiology review identified in the last row of the table. The 11/1/2018 date should also be corrected to 11/2/2018.

(b) (4)

(b) (4)

These revisions and clarifications do not alter the conclusion of the review that the application is approvable from a microbiology perspective or the scientific thinking underlying that conclusion.

Paul Dexter

Digitally signed by Paul Dexter
Date: 1/28/2022 02:08:15PM
GUID: 508da70c00028f8ef6fc7fb5f60df2ce

Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 1/28/2022 02:10:47PM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

ANDA 205894

DISCIPLINE REVIEW LETTER
LABELING

Mylan Pharmaceuticals Inc., a Viatris Company
3711 Collins Ferry Road
Morgantown, WV 26505
Attention: Wayne Talton

Dear Wayne Talton:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 26, 2021, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cyclosporine Ophthalmic Emulsion, 0.05%.

The following possible deficiencies have been identified by LABELING:

PRESCRIBING INFORMATION; FULL PRESCRIBING INFORMATION

A. 11 DESCRIPTION: Revise your structural formula with the same presentation as the reference listed drug (RLD) labeling.

B. 16 HOW SUPPLIED/STORAGE AND HANDLING
   i. Delete 1st paragraph, “Cyclosporine ophthalmic emulsion is a sterile white opaque to slightly translucent homogenous emulsion of 0.05% cyclosporine, USP.”
   ii. Revise the 2nd paragraph, first sentence to read, Cyclosporine ophthalmic emulsion, 0.05% is packaged in sterile, preservative-free single-use vials.” (replace (b) (4)” with “packaged” and delete (b) (4)”).

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United

States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than January 21, 2022. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

[1] GDUFAD Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Carol Lee, Labeling Project Manager, at Carol.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Carol Lee, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Carol Lee

Digitally signed by Carol Lee
Date: 1/19/2022 10:51:33AM
GUID: 5509900500075ef5af0b093081e71363

ANDA 205894

INFORMATION REQUEST

Mylan Pharmaceuticals Inc, a Viatris Company
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310 USA

Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Wayne Talton:

This is in reference to your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C) for Cyclosporine Ophthalmic Emulsion 0.05%.

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product. See 21 CFR Part 3.

Should you disagree with the assessment that your proposed product is a combination product, you may contact the Office of Combination Products (OCP) at combination@fda.gov.

We are reviewing the Quality section of your submission and have the following comments and information requests.

- Since your proposed product is considered a drug-device combination product as noted above, for each submission for this application indicate that the product is a combination product in field #24 of the Form FDA 356h. Additionally, please refer to the Guidance for Industry Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers (October 2019). For combination products, facilities manufacturing a constituent part of a co-package or single-entity combination product, or drug-device combination

product that are proposed to be involved in the disposition of commercial product should be included on Form FDA 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.

- We could not locate information on comparative drop size (weight or volume) study for your drug product. Please provide comparative drop size data for your proposed container closure system using multiple lots of your test product and RLD.

In addition, we have the following general comment:

- Combination products are subject to the current good manufacturing practice (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements as specified in 21 CFR 601.2(d).

  If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.

  Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

We request a prompt written response, no later than **November 1, 2021** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Temitope Oriola, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

[*See appended electronic signature page]*

Temitope Oriola, PharmD
Regulatory Business Process Manger
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Temitope Oriola

Digitally signed by Temitope Oriola
Date: 10/21/2021 04:58:53PM
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ANDA 205894

INFORMATION REQUEST

Mylan Pharmaceuticals Inc
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Wayne Talton:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 17, 2020, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Cyclosporine Ophthalmic Emulsion, 0.05%.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug Product

(b) (4)

We request a prompt written response, no later than **July 25, 2021** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an

amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Temitope Oriola

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Date: 7/20/2021 03:23:29PM
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ANDA 205894

INFORMATION REQUEST

Mylan Pharmaceuticals Inc
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Wayne Talton:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 17, 2020, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Cyclosporine Ophthalmic Emulsion, 0.05%.

We are reviewing the Quality section of your submission and have the following comments and information requests:

(b) (4)

We request a prompt written response, no later than **July 15, 2021** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Temitope Oriola

Digitally signed by Temitope Oriola
Date: 6/25/2021 12:46:02PM
GUID: 56f4536500ea9700421d7152e24f140d

ANDA 205894

INFORMATION REQUEST

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on November 1, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Cyclosporine Ophthalmic Emulsion, 0.05%.

Reference is also made to your amendment dated December 17, 2020.

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

FDA has insufficient information to determine whether any differences in design for the user interface of your proposed generic product as compared to the reference listed drug (RLD) are acceptable and whether your product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. One consideration is whether the proposed product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use.

Specifically, we request additional information regarding the proposed user interface for your product as compared to the user interface of the RLD. One way of providing information to assist us in evaluating the user interface of your proposed product as compared to the user interface of the RLD would be to submit to your ANDA the results of three comparative analyses (e.g., comparative labeling analysis, comparative task analysis, and comparison of design of the delivery device part), as well as your overall assessment of any identified differences for your proposed product when compared to the RLD. For background information on providing this type of information, see the draft guidance for industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), available at https://www.fda.gov/media/102349/download. Depending on the results of the comparative analyses discussed in this draft guidance, submission of additional data may be warranted, such as data from comparative use

human factors studies, to assess the acceptability of differences identified in the user interface for your proposed product. As always, you can use an alternative approach to providing this information if it satisfies the requirements of the applicable statutes and regulations for approval.

We also provide the following recommendations:

(b) (4)

- If you believe that comparative analyses are not applicable to your specific ANDA, provide the appropriate justification within your response as to why you believe that comparative analyses are not applicable to your product and, if appropriate, include an alternative approach that addresses the issues outlined in this letter.
- Due to concerns related to COVID-19, we are unable to request and access any physical product samples at this time. Therefore, in lieu of submitting the physical samples, please submit high-resolution color photos of each size and strength of the to-be marketed proposed product and of each corresponding size and strength of the RLD. Photos should include several angles of all aspects of the products, including photos of the dropper bottle and tip with and without cap removed. The proposed product should be affixed with the to-be-marketed immediate container label, or a label that closely resembles the to-be marketed product. For the proposed product, samples with a mocked label, i.e., non-commercially produced, depicting the actual label in both size, shape and font would be acceptable. In the future, the Agency may request physical product samples, if needed. This request is separate from any request for samples that may come to you from the Office of Pharmaceutical Quality.
- Please contact FDA as described below for questions regarding specific submission needs, including test and RLD samples or pictures.

We request a complete written response no later than November 5, 2021, in order to continue our evaluation of your ANDA. Facsimile or e-mail responses will not be accepted. When you submit your response to the IR, prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESPONSE TO IR: COMPARATIVE ANALYSES / CLINICAL

If you do not submit a complete written response by November 5, 2021 the listed information requests may be incorporated in a complete response letter.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted

in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions with regard to this matter, please contact Nitin K. Patel, Division of Clinical Review at Nitin.Patel@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Nitin K. Patel, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Safety and Clinical Evaluation
Office of Generic Drugs
Center for Drug Evaluation and Research

Nitin K. Patel

Digitally signed by Nitin K. Patel
Date: 10/22/2021 09:51:18AM
GUID: 508da70c00028f695d87f612d0d4cbb6

ANDA 205894

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This is in reference to your amendment received on May 26, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Cyclosporine Ophthalmic Emulsion, 0.05%.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is August 25, 2021.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact LCDR Daniil Marchuk, Regulatory Project Manager, at (240) 402 - 4322.

Sincerely,

{See appended electronic signature page}

Daniil Marchuk, PharmD, BCPS
LCDR, USPHS
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Daniil Marchuk

Digitally signed by Daniil Marchuk
Date: 6/02/2021 10:41:58AM
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M E M O R A N D U M

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

DATE: 3/4/2021

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: ANDA 205894

The Division of Generic Drug Study Integrity (DGDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs (b) (4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	Mylan Laboratories, Ltd.	Clinical Research Centre, Saradhi Chambers, A-4, Near Poulomi Hospital, Main Road, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad, Telengana, India

ANDA 205894

POST-CRL MEETING
MEETING MINUTES

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on November 1, 2013, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Cyclosporine Ophthalmic Emulsion, 0.05%.

We also refer to the meeting between the applicant and FDA on October 25, 2019. The purpose of the meeting was to provide Mylan a listening only teleconference opportunity to communicate the data and information submitted to the Agency in their Meeting Request received on September 27, 2019.

A copy of the official minutes of the post-CRL meeting is enclosed for your information. Please notify the Agency in writing via the Electronic Submissions Gateway of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LT Daniil Marchuk, Regulatory Project Manager at (240) 402- 4322.

Sincerely,

{See appended electronic signature page}

Daniil Marchuk, PharmD, BCPS
LT, USPHS
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Post-complete response letter meeting

Meeting Date and Time: October 25, 2019
9:05 am to 10:35 am (EST) [ended at 10 am]

Application Number: 205894
Product Name: Cyclosporine Ophthalmic Emulsion, 0.05%
Applicant Name: Mylan Pharmaceuticals Inc.

Meeting Recorder: Daniil Marchuk

FDA ATTENDEES

Sally Y. Choe, Director, Office of Generic Drugs (OGD)
Kristin Davis, Acting Director, Office of Generic Drug Policy (OGDP), OGD
Christopher Pruitt, Acting Deputy Director, OGDP, OGD
Lesley DeRenzo, Regulatory Counsel, Division of Legal and Regulatory Support, OGDP, OGD
Robert Lionberger, Director, Office of Research and Standards (ORS), OGD
Lei Zhang, Deputy Office Director, ORS, OGD
Darby Kozak, Lead Chemist, Division of Therapeutic Performance, ORS, OGD
Bing Li, Acting Office Director, Office of Bioequivalence (OB), OGD
Nilufer Tampal, Acting Deputy Office Director, OB, OGD
Martin Yoon, Project Manager Team Leader, OB, OGD
Utpal Munshi, Division Director, Division of Bioequivalence I (DBI), OB, OGD
Hee Sun Chung, Lead Pharmacologist, DBI, OB, OGD
Amanda Jones, Acting Lead Pharmacologist, DBI, OB, OGD
Hongling Zhang, Acting Division Director, DBII, OB, OGD
Minglei Cui, Lead Pharmacologist, DBII, OB, OGD
Jennifer Miller, Lead Pharmacologist, DBII, OB, OGD
Josephine Aimiuwu, Pharmacologist, DBII, OB, OGD
Lanyan (Lucy) Fang, Acting Division Director, DBIII, OB, OGD
Ke Ren, Associate Director, DBIII, OB, OGD
Chyong-Yi Wu, Regulatory Health Project Manager, DBIII, OB, OGD
Krishna Chimalakonda, Visiting Associate, DBIII, OB, OGD
Bing Cai, Director, Division of Liquid-based Products (DLBP), Office of Lifecycle Drug Products (OLDP), Office of Pharmaceutical Quality (OPQ)
Asif Rasheed, Senior Reviewer, DLBP, OLDP, OPQ
Patricia Onyimba, Branch Chief, Liquid-Based Branch I (LBBI), DLBP, OLDP, OPQ
Andre Raw, Senior Scientific and Policy Advisor, OLDP, OPQ

Mohamed Ghorab, Branch Chief, Division of Regulations, Guidance, & Standards (DRGS), Office of Policy for Pharmaceutical Quality (OPPQ), OPQ
Yaodong Huang, Acting Quality Assessment Lead, Process Assessment Branch VI, Division of Process Assessment II, Office of Process & Facilities, OPQ
Xiaoming Xu, Senior Chemist, Division of Product Quality Research, Office of Testing & Research, OPQ
Edward Sherwood, Director, Office of Regulatory Operations (ORO), OGD
Sarah Kurtz, Associate Director for Application Quality, ORO, OGD
Anh Pham, Associate Director for Operations, ORO, OGD
Andrew Kim, Supervisory Regulatory Project Manager, Division of Project Management (DPM), ORO, OGD
Daniil Marchuk, Regulatory Project Manager (RPM), DPM, ORO, OGD
Honghong La, RPM, DPM, ORO, OGD
Meenu Sharma, RPM, DPM, ORO, OGD

APPLICANT ATTENDEES

Wayne Talton, Head of Global Regulatory Affairs
Andrea Miller, Head of Global Research and Development and Regulatory Affairs
Walt Owens, Head of Respiratory and Biologics Operations
Pat Vallano, Head of Innovative Programs
Brian Stone, Counsel, Global Regulatory
Sanjeev Sethi, Chief Operating Officer
Ajay Singla Head of Global Injectables R&D and Scientific Affairs
Nitin Bhattad, Head of Regulatory Science, Injectables
Shashikant Tiwari, Head of Analytical Services, Injectable R&D
Carmen Shepard, Consultant

A. BACKGROUND

The purpose of the meeting was to provide Mylan a listening only teleconference opportunity to communicate the data and information submitted to the Agency in their Meeting Request received on September 27, 2019.

B. DISCUSSION

Mylan presented slides 1-21 and provided background information and scientific data regarding Mylan Mylan’s Cyclosporine Ophthalmic Emulsion ANDA 205894.

No decisions made during this meeting.

D. ACTION ITEMS

Agree to meet for a teleconference with ORO in a week for any new updates the agency can provide. Scheduled for October 30, 2019.

E. ATTACHMENTS AND HANDOUTS

Mylan provided slides for this meeting titled “Mylan’s Cyclosporine Opthalmic Emulsion, 0.05%, ANDA 205894, Scientific Discussion Meeting, October 25, 2019”.

Daniil Marchuk

Digitally signed by Daniil Marchuk
Date: 10/29/2020 02:03:13PM
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Memorandum

To: **Abbreviated New Drug Application (ANDA) 205894 from Mylan Pharmaceuticals for Cyclosporine Ophthalmic Emulsion 0.05%**

From: **April Braddy, PhD, RAC**
Acting Director
Division of Bioequivalence III
Office of Bioequivalence, Office of Generic Drugs
Center for Drug Evaluation and Research, US Food and Drug Administration

Patricia Onyimba, MS
Branch Chief
Branch 1, Division of Liquid Based Products I
Office of Lifecycle Drug Products, Office of Pharmaceutical Quality
Center for Drug Evaluation and Research, US Food and Drug Administration

Date: **September 29, 2020**

Subject: **Q2 Assessment** (b) (4)

The purpose of this memorandum is to document the Office of Generic Drug's (OGD's) and Office of Pharmaceutical Quality's (OPQ's) assessment that ANDA 205894 is not quantitatively the same as the reference listed drug (RLD), RESTASIS® Cyclosporine Ophthalmic Emulsion, 0.05% (NDA 050790), with respect to the quantity (b) (4)

I. Background

The Food and Drug Administration ("FDA" or "the Agency") will refuse to approve an ANDA if it determines that "the inactive ingredients of the drug are unsafe for use" as labeled, or if "the composition of the drug is unsafe … because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included."[1] Under applicable regulations, for a proposed generic version of an ophthalmic drug, the Agency "will refuse to approve the ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, substances to adjust tonicity, or thickening agents, in the same concentration" as the RLD.[2] FDA has interpreted "same concentration" in this regulation (which also applies to otic products) and a similar regulation governing parenteral products to mean that the concentration of each inactive ingredient used in the generic

[1] Section 505(j)(4)(H) of the FD&C Act; see also 21 CFR 314.127(a)(8)(i).
[2] 21 CFR 314.127(a)(8)(ii)(C); see also 21 CFR 314.94(a)(9)(iv). FDA refers to these listed types of inactive ingredients collectively as *exception excipients*.

product must be within ± 5% of the concentration of that ingredient used in the RLD.[3] FDA generally refers to two drug products (usually an ANDA and its RLD) that have the same inactive ingredients as qualitatively (Q1) the same and, if those same inactive ingredients are in the same concentration, as quantitatively (Q2) the same.

(b) (4)

II. Composition of ANDA 205894

ANDA 205894 (b) (4)

[3] See, e.g., Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards, at 8-9 (Dec. 2016) (stating that "same implies ≥95% but ≤105% of the RLD concentration or amount"), available at https://www.fda.gov/media/86660/download; FDA Citizen Petition Response re: Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) otic suspension (Docket no. FDA-2016-P-2782) at 4 (Feb. 10, 2017) ("Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product."). See also FDA Citizen Petition Response re: Vancocin Hydrochloride (vancomycin hydrochloride) 125 mg and 250 mg oral capsules (Docket no. FDA-2006-P-0007) at 35 (Apr. 9, 2012) ("'Quantitatively the same' has been determined by CDER, in the context of locally acting drugs, to mean that the concentration or amount of the inactive ingredient(s) in the test product would not differ by more than '5 percent of the concentration or amount in the reference listed drug'"); and FDA Citizen Petition Response re: Derma-Smoothe/FS (fluocinolone acetonide) 0.01% Topical Oil (Docket no. FDA-2004-P-0215) at 13 (Mar. 25, 2009) ("[A product] will be considered Q2 if the concentration or amount of each of [the inactive] ingredients differs from the concentration or amount of the same ingredient in the RLD by no more than 5 percent of that ingredient."), both citing FDA's draft guidance for industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (Apr. 2003), at 8, available on FDA's web site at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-and-bioequivalence-studies-nasal-aerosols-and-nasal-sprays-local-action (last visited Apr.15, 2020).

[4] Such consideration of qualitative and quantitative sameness is also consistent with the in vitro option described in a draft product specific guidance ("PSG") for cyclosporine ophthalmic emulsion to demonstrate bioequivalence of a proposed generic cyclosporine emulsion product to the RLD. See Draft Guidance on Cyclosporine (rev. Oct. 2016), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%20050790_RV09-16.pdf. ANDA 205894 seeks to employ the in vitro option described in the draft PSG.

[5] See NDA 050790, Seq 0147 (submitted on 11/03/2015) and Seq 0119 (submitted on 04/11/2012) (b) (4) in composition table. Also, see quality review for S-024 which indicates that the composition and strength of cyclosporine ophthalmic emulsion 0.05% supplied in the new container closure system (multi-dose, proposed in the supplement) remain unchanged from the currently approved presentation (unit-dose).

(b) (4)

[7] GS Review: ANDA 205894, Bioequivalence/Response to Information Request, 07/10/2019, Module 3.2.P.1.

(b) (4)

III. Previous Review Statements and Communications (b) (4)

(b) (4)

- FDA's 08/24/2011 response by telephone to Controlled Correspondence 11-0183, in which FDA stated that one of the proposed formulations was acceptable for filing. (b) (4)
- The original bioequivalence (BE) review[11] stated that amount of inactive ingredients in the proposed test product are within ±5% of the RLD and considered acceptable. This statement in the original BE review implied that the formulation of the proposed test product is Q1/Q2 the same as the RLD and is considered acceptable.

(b) (4)

(b) (4)

[9] The list below is intended to be comprehensive. To the extent a statement in the record for ANDA 205894 that is inconsistent with this memorandum was inadvertently omitted, however, that statement also is superseded by this memorandum.

[10] Control 11-0183, *Office of Generic Drugs Control Document Tracking Control Form: Control #: 11-0183,* Aug. 24, 2011, at \\fda.gov\wodc\CDER\OGD\All\OGDS6\Controls\2011-docs\11-0183.pdf

[11] ANDA 205894, Bioequivalence Primary Review, *A205894N000DB_N11012013.docx,* Nov. 2, 2016, at http://panorama.fda.gov/task/view?ID=542124870034e8954709b1d5fdbbfa41.

[12] ANDA 205894, Complete Response Letter, *205894_ANDA_CRL.docx*, Dec. 08, 2016, at https://panorama.fda.gov/task/view?ID=576f3781009635da892cea86499c9af6.

April Braddy

Digitally signed by April Braddy
Date: 9/29/2020 12:31:00PM
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Patricia Onyimba

Digitally signed by Patricia Onyimba
Date: 9/29/2020 12:57:59PM
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MEMORANDUM OF MEETING MINUTES

Meeting Type: Status Update Teleconference

Meeting Date and Time: January 17, 2020 / 2:05pm – 3:00pm (EST)

Application Number: 205894
Product Name: Cyclosporine Ophthalmic Emulsion, 0.05%
Applicant Name: Mylan Pharmaceuticals Inc.

Meeting Recorder: Daniil Marchuk

MYLAN ATTENDEES

Rajiv Malik, President
Andrea Miller, Head of Global R&D and Regulatory Affairs
Wayne Talton, Head of Global Regulatory Affairs
Walt Owens, Head of Global Biologics and Respiratory Science & Operations
Ajay Singla Head of Global Injectables R&D and Scientific Affairs
Carmen Shepard, Consultant
Brian Stone, Counsel, Global Regulatory

FDA ATTENDEES

Sally Y. Choe, Ph.D., Director, Office of Generic Drugs (OGD)
Iilun C. Murphy, M.D., Deputy Director for Clinical and Regulatory Affairs, OGD
William Chong, M.D., Acting Associate Director of Clinical Affairs, OGD
Tawni Schwemer, Acting Senior Advisor, OGD
Cassandra Desnoes, Special Assistant, OGD
Maryll Toufanian, J.D., Director, Office of Generic Drug Policy, OGD
Edward Sherwood, Director, Office of Regulatory Operations (ORO), OGD
Anh Pham, Pharm.D., Associate Director for Operations, ORO, OGD
Andrew Kim, Pharm.D., Supervisory Regulatory Project Manager, Division of Project Management, ORO, OGD
Daniil Marchuk, Pharm.D., Regulatory Project Manager, Division of Project Management, ORO, OGD

A. BACKGROUND

This is a follow up teleconference meeting regarding

ANDA 205894
Drug Product – *Cyclosporine Ophthalmic Emulsion, 0.05%*
Applicant – Mylan Pharmaceuticals Inc.

The purpose of this follow up teleconference meeting is to provide a status update on the discipline reviews for the unapproved ANDA 205894.

B. STATUS UPDATE

Mylan: Presented slides 1-16 and provided background information pertaining to Mylan's Cyclosporine Ophthalmic Emulsion ANDA. Mylan highlighted the history of their application, the cost impact to public health for not having generic alternatives on the market, Mylan's costs, and various regulatory and scientific challenges that were overcome since the receipt of the application by the Agency on November 1, 2013.

Mylan also expressed concerns regarding the timeline, transparency, and clarity from FDA to get this generic application approved. Shared the perspective on the need for predictability and is ready to assist the Agency in addressing any outstanding concerns.

FDA: Expressed appreciation for the background information, and the detailed presentation of the impact of this drug product on Mylan, and the American public.

FDA hears and understands Mylan's frustrations. FDA also shares the same common goal of bringing generic alternatives to the market and making them available to the patients, and particularly, this drug product which has faced some challenges. Despite these challenges, this application remains a top priority for FDA. The Agency is 100% committed to helping to move this application through the review process and is putting a lot of concerted effort to overcome various issues. While these efforts are ongoing, FDA cannot share the specifics of the issues or provide you with a timeline at this point.

Upon further development, the Agency will reevaluate what information may be shared with Mylan in regard to pending issues.

C. ACTION ITEMS

Agree to meet for a teleconference with ORO in a week for any new updates the agency can provide. (Scheduled for January 24, 2020.)

Daniil Marchuk

Digitally signed by Daniil Marchuk
Date: 2/05/2020 10:20:48PM
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ANDA 205894

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This is in reference to your amendment received on June 29, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Cyclosporine Ophthalmic Emulsion, 0.05%.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is December 28, 2018. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence (PFC) was not submitted or not accepted, the GDUFA goal date for review of this priority major amendment is April 28, 2019.

If you have any questions, contact Daniil Marchuk, Regulatory Project Manager, at (240) 402-4322.

Sincerely,

{See appended electronic signature page}

Daniil Marchuk
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Daniil Marchuk

Digitally signed by Daniil Marchuk
Date: 8/08/2018 03:36:30PM
GUID: 5991f04600226cbe8bbec8ebcb9cae54

ANDA 205894

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This is in reference to your amendment received on June 29, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Cyclosporine Ophthalmic Emulsion, 0.05%.

Reference is also made to the amendment acknowledgement letter issued on August 8, 2018 in error. This corrected letter changes the classification from priority review to standard review and replaces the amendment acknowledgement issued on August 8, 2018.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment. We acknowledge that you have requested a priority review for this submission. However, your submission does not meet the criteria in accordance with the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is February 27, 2019. If FDA determines that an inspection is required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is April 28, 2019.

If you have any questions, contact Daniil Marchuk, Regulatory Project Manager, at (240) 402 - 4322.

Sincerely,

{See appended electronic signature page}

For Daniil Marchuk
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Anh
Pham, Pharm.D.

Digitally signed by Anh Pham, Pharm.D.
Date: 8/31/2018 11:57:27AM
GUID: 54e4c56f00060bb2c61b878bc7a7bf95

ANDA 205894

COMPLETE RESPONSE

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310
Attention: Wayne Talton
Head of Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on November 1, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Cyclosporine Ophthalmic Emulsion, 0.05%.

We acknowledge receipt of the February 8, 2017 submission, which constituted a complete response to our December 8, 2016 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

(b) (4)

(b) (4)

BIOEQUIVALENCE

Your in vitro drug release testing (IVRT) study (No. CPS-IVR-Part IV) using the rotating bottle dissolution apparatus is inadequate. As requested previously in the IR dated September 20, 2017, please provide information on mass balance of castor oil and polysorbate 80 in the aqueous and isobutyl acetate layers from your proposed test product and the reference listed drug (RLD) product; Restasis®, over the complete duration of the IVRT study.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

MICROBIOLOGY / LABELING / FACILITY INSPECTIONS/EVALUATIONS

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be reevaluated upon resubmission.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia - National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling. It is also your responsibility to ensure that your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY / BIOEQUIVALENCE

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, call Anh Pham, Regulatory Project Manager, Division of Project Management, at (240) 402-4686.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Andrew Kim

Digitally signed by Andrew Kim
Date: 5/21/2018 03:38:44PM
GUID: 508da70600028aaa57d6fc4456bcd799

Internal Meeting Minutes

Date:	July 19, 2017
Time:	2:00 PM – 3:00 PM
Meeting Location:	Bldg. 75, Room 4600

Drug Product:	ANDA 205894: Cyclosporine ophthalmic emulsion, 0.05%, Bioequivalence amendment & Dissolution Review ANDA 205078: Sitagliptin Phosphate and Metformin HCl ER Tablets, Dissolution Amendment
RLD:	Restasis® (NDA 050790) for ANDA 205894 Janumet XR® (NDA 202270) for ANDA 205078

Attendees:

Division of Bioequivalence III (DB III)
Nilufer Tampal, Ph.D., Director, Division of Bioequivalence (DB) III
April Braddy, Ph.D., Deputy Director, DBIII
Ke Ren, Ph.D., Associate Director, DBIII
Svetlana Cherstniakova, Ph.D., Team Leader, DBIII
Krishna Chimalakonda, Ph.D., Reviewer, DBIII (*Presenter & Meeting Recorder*)
Pariban Dhanormchitphong, Pharm.D., Project Manager TL, DBIII
Moheb Makary, Ph.D., Team Leader, DBIII
Li Gong, Ph.D., Team Leader, DBIII
Li Xia, Ph.D., Team Leader, DBIII
Wendy Cai, Ph.D., Team Leader, DBIII
Manjinder Kaur, Ph.D., Reviewer, DBIII (filling-in for Suman Dandamudi, Ph.D., Team Leader, DBIII)

Purpose:

The review team for ANDA 205894 would like to get management's concurrence to send a consult to the Office of Research Standards (ORS) to conduct statistical analysis to establish bioequivalence between the test product, cyclosporine ophthalmic emulsion, 0.05% and the RLD, Restasis®. (b) (4) .

Background:

For ANDA 205894, the test product is cyclosporine ophthalmic emulsion, 0.05% and the reference listed drug (RLD) product is Restasis® (cyclosporine) ophthalmic emulsion, 0.05%. The draft product specific guidance for this drug product was revised in Oct. 2016. In response to the complete response (CR) letter, the firm submitted complete globule size distribution (GSD) validation data, pivotal GSD data generated using high-

resolution (narrow mode), and conducted statistical analysis using earth mover distance (EMD) method. In addition, the firm also submitted in vitro release testing (IVRT) method development and validation report along with pivotal IVRT data generated using rotating bottle dissolution apparatus.

(b) (4)

Questions:

ANDA 205894

The review team requests management's concurrence to send a consult to ORS for conducting statistical analysis.

(b) (4)

Discussion:

ANDA 205894

Management agreed to send the consult to ORS for statistical analysis. There was a discussion about SAS training to conduct EMD analysis in the future for reviewers in DB III. In addition, the feasibility to get SAS code from ORS was also discussed. Management further touched upon the idea of a request from the Office of Bioequivalence (OB) to ORS to get the SAS code for EMD analysis. A question was posed to the presenter if GSD data is different between general purpose and narrow modes and the reviewer answered in the affirmative.

(b) (4)

Action Items:

- For ANDA 205894, the review team will send consult to ORS for EMD analysis.

(b) (4)

Drafted by Krishna Chimalakonda on 07/20/2016 (Primary reviewer)
Revised by Svetlana Cherstniakova (Secondary reviewer)
Reviewed by April Braddy (Tertiary reviewer)

Attachments:

ANDAs 205894 and 205078 Amendment.p	DBIII MM Review Template.docx

[1] GDRP ANDA 203658-Orig-1, Biopharmaceutics Primary Review, Jinzhe Mao, 10/31/14. Last accessed on 7/31/17

http://panorama.fda.gov/task/view?ID=54212ee0003f8bb7679f3cf71b83a097

OFFICE OF RESEARCH AND STANDARDS (ORS)
DIVISION OF THERAPEUTIC PERFORMANCE (DTP)

RESPONSE TO CONSULT REQUEST

From:	Peter Petrochenko, PhD, CDER/OGD/ORS/DTP
Through:	Darby Kozak, PhD, Team Lead, CDER/OGD/ORS/DTP Xiaohui Jiang, PhD, Deputy Director, CDER/OGD/ORS/DTP
To:	Nilufer M. Tampal, Ph.D. Director, Division of Bioequivalence III, Office of Bioequivalence, Office of Generic Drugs
Submission Type:	ANDA Review (ANDA-205894) 0.05% Cyclosporine Ophthalmic Emulsion; Applicant: Mylan Pharmaceuticals. 07/21/2016 (submission of additional BE and drug release data) 02/08/2017 (Response to CR)
Reference No.	13087958
Submission Date:	07/25/2017
Subject:	Consult response to comment on the acceptability of the in vitro release test method used by the applicant, Mylan Pharmaceuticals in ANDA-205894

1. BACKGROUND

This consult is from the Division of Bioequivalence III (DBIII), Office of Bioequivalence, Office of Generic Drugs regarding the in vitro release testing (IVRT) method proposed by Mylan Pharmaceuticals (the Firm) in ANDA 205894, for their cyclosporine ophthalmic emulsion, 0.05% test product. The reference-listed drug (RLD) is Restasis® (cyclosporine) ophthalmic emulsion, 0.05% developed by Allergan Pharmaceuticals and approved on 23 December 2002 under NDA 050790. Restasis is a topical ophthalmic drop administered twice daily and is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

The current product specific guidance (PSG)[1] recommends firms either conduct comparative in vitro testing or an in vivo clinical endpoint study to demonstrate bioequivalence (BE) of a Test product to the RLD. There is currently no USP or FDA-recommended IVRT method for this drug product. Thus, the PSG recommends that applicants develop an in vitro drug release method capable of discriminating the effect of process variability in the production of the test formulation.

As of 09/09/2016 there are no approved but (b) (4) ANDAs under review for this product: 203880 (P), (b) (4) 205894 (P), (b) (4), 209064 (P), (b) (4) ANDA 205894 from Mylan, the ANDA in question, has a current Target Action Date (TAD) of 09/20/2017. In this ANDA the Firm proposes an 'extraction' IVRT method (b) (4) (b) (4)

[1] Draft guidance on cyclosporine: Recommended Jun 2013; Revised Feb 2016; Oct 2016
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf

(b) (4)

In the earlier Complete Response (CR) letter for this ANDA (ANDA 205894), dated 12/08/2016, the Firm was asked to submit pre-study method development and validation data for their proposed rotating bottle IVRT method. The Firm submitted the IVRT method development report and conducted IVRT validation with rotating bottle dissolution apparatus in the amendment dated 02/08/2017, module 1.12.15. The Firm also submitted the pivotal IVRT data with rotating bottle dissolution apparatus using 3 lots of the test (Nos. 01813A, 01813B, 03912A) and RLD (Nos. 80773, 80796, 81028) products.

Per the current pending BE review[2], the data submitted in the IVRT method development and validation report currently appears adequate to demonstrate the suitability of rotating bottle dissolution apparatus to evaluate comparative in vitro release of the test product and the RLD. The pending Dissolution Review[3] also concluded that the IVRT data appears acceptable, but that the Firm should propose release specifications. The BE Reviewer recommends the Firm acknowledge the following drug release method and specifications:

Time (min)	% drug release
5	NMT (b) (4) %
30	(b) (4) %
120	NLT (b) (4) %

DBIII sent this consult request to Office of Research and Standards (ORS) to get ORS comment and feedback on the acceptability of the IVRT method proposed in ANDA 205894. If deemed unacceptable, ORS will help identify potential limitations and deficiencies with the approach for DBIII to communicate to the Firm.

2. CONSULT REQUEST

DBIII questions/requests for DTP:

Q1. Please comment on the suitability of the proposed IVRT method using rotating bottle dissolution apparatus for comparative drug release testing to establish bioequivalence (BE) and methodology to compare drug release profiles between the test product and RLD by calculating the similarity (f2) value. Please provide deficiencies or comments, as appropriate that need to be communicated to the firm, if any.

Q2. If IVRT method is used as a routine release test for quality control (QC) purpose, please comment on the suitability of the proposed IVRT method and drug release specifications (shown

[2] GDRP ANDA 205894-Orig-1-Amend-31, Bioequivalence Primary Review, Krishna Chimalakonda, 06/08/17
http://panorama.fda.gov/task/view?ID=589e26ac00a52c5d7aa2620aa12f9b81
[3] GDRP ANDA 205894-Orig-1-Amend-31, Dissolution Review, Krishna Chimalakonda
http://panorama.fda.gov/document/preview?versionID=59513590002fedca209b4ae444d18bc3&ID=594bc92f004044b160eaf4a73ba2e39b

(b) (4)

the commercial batch. Please refer to the revised draft guidance on Cyclosporine ophthalmic emulsion (revised in February 2016) for Agency's recommendation on the size of the exhibit batches.

Reviewed by:
Mohammad (Abir) Absar, PhD
Division of Therapeutic Performance, ORS/OGD

Concurred by:
Stephanie Choi, PhD
Acting Team Lead, Division of Therapeutic Performance, ORS/OGD

&

Markham Luke, MD, PhD
Acting Director, Division of Therapeutic Performance, ORS/OGD

APPENDIX A

DPQRTR_FY16_015_C
yclosporine_Final Rep