CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207606 Orig1sS000

Trade Name: Cyclosporine Ophthalmic Emulsion, 0.05%.

Sponsor: Apotex Corp.

Approval Date: January 12, 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

207606Orig1sS000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207606Orig1s000

APPROVAL LETTER

ANDA 207606

ANDA APPROVAL

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 18, 2014, 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 May 27, 2022, 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 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.

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[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 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

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

Sarah Kurtz

Digitally signed by Sarah Kurtz
Date: 1/12/2023 05:08:52PM
GUID: 54078879000a1b9e15dd31ed6f0343ca

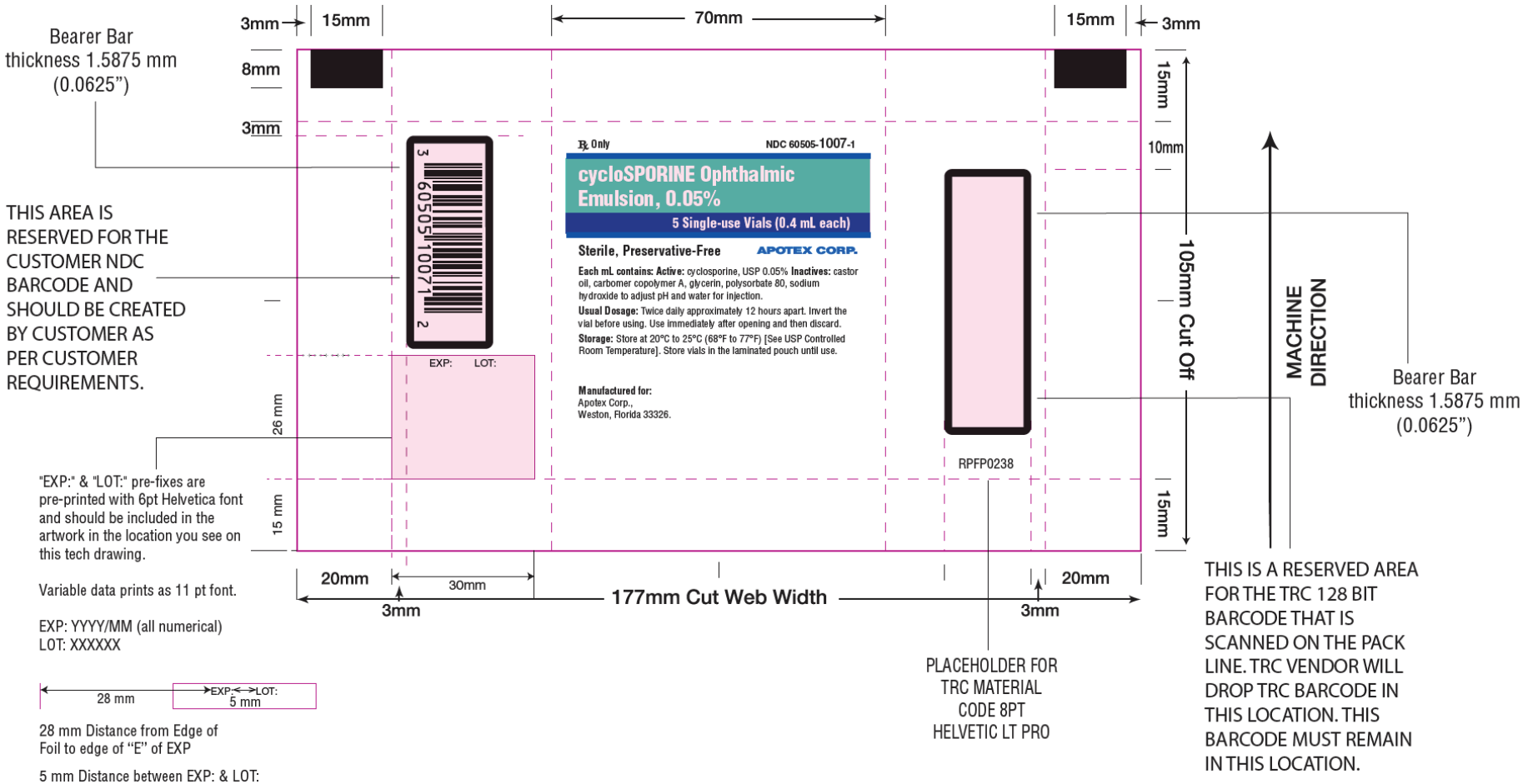
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

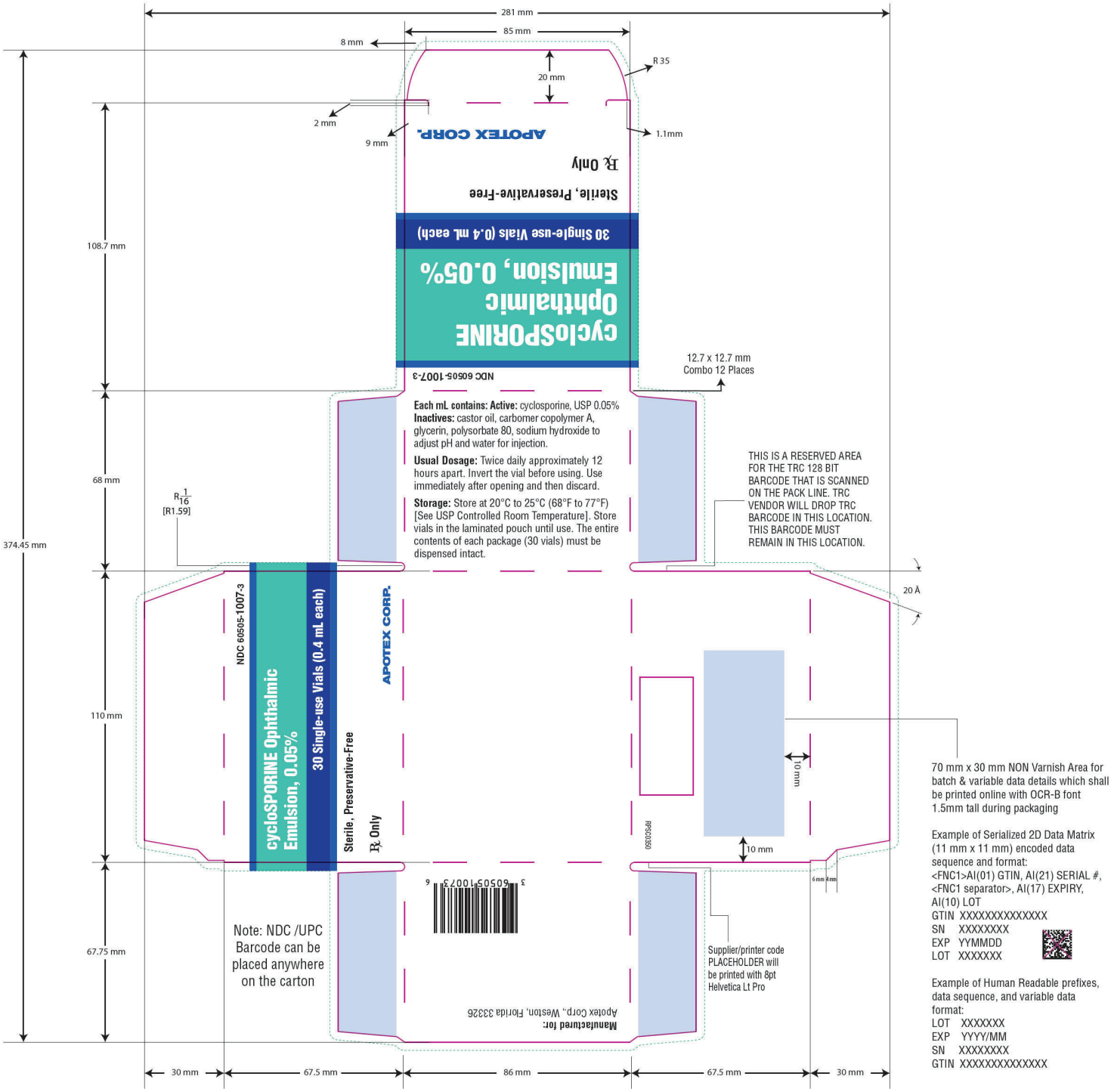
207606Orig1s000

LABELING

(b) (4)


Bearer Bar
thickness 1.5875 mm
(0.0625")
THIS AREA IS RESERVED FOR THE CUSTOMER NDC BARCODE AND SHOULD BE CREATED BY CUSTOMER AS PER CUSTOMER REQUIREMENTS.
"EXP:" & "LOT:" pre-fixes are pre-printed with 6pt Helvetica font and should be included in the artwork in the location you see on this tech drawing.
Variable data prints as 11 pt font.
EXP: YYYY/MM (all numerical)
LOT: XXXXXX
28 mm
EXP:
LOT:
5 mm
28 mm Distance from Edge of Foil to edge of "E" of EXP
5 mm Distance between EXP: & LOT:
3mm
15mm
70mm
15mm
3mm
8mm
3mm
15mm
10mm
105mm Cut Off
15mm
26 mm
15 mm
20mm
30mm
177mm Cut Web Width
3mm
20mm
3mm
Rx Only
NDC 60505-1007-1
cycloSPORINE Ophthalmic Emulsion, 0.05%
5 Single-use Vials (0.4 mL each)
Sterile, Preservative-Free
APOTEX CORP.
Each mL contains: Active: cyclosporine, USP 0.05% Inactives: castor oil, carbomer copolymer A, glycerin, polysorbate 80, sodium hydroxide to adjust pH and water for injection.
Usual Dosage: Twice daily approximately 12 hours apart. Invert the vial before using. Use immediately after opening and then discard.
Storage: Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. Store vials in the laminated pouch until use.
Manufactured for:
Apotex Corp.,
Weston, Florida 33326.
RPFP0238
PLACEHOLDER FOR TRC MATERIAL CODE 8PT HELVETIC LT PRO
MACHINE DIRECTION
Bearer Bar
thickness 1.5875 mm
(0.0625")
THIS IS A RESERVED AREA FOR THE TRC 128 BIT BARCODE THAT IS SCANNED ON THE PACK LINE. TRC VENDOR WILL DROP TRC BARCODE IN THIS LOCATION. THIS BARCODE MUST REMAIN IN THIS LOCATION.

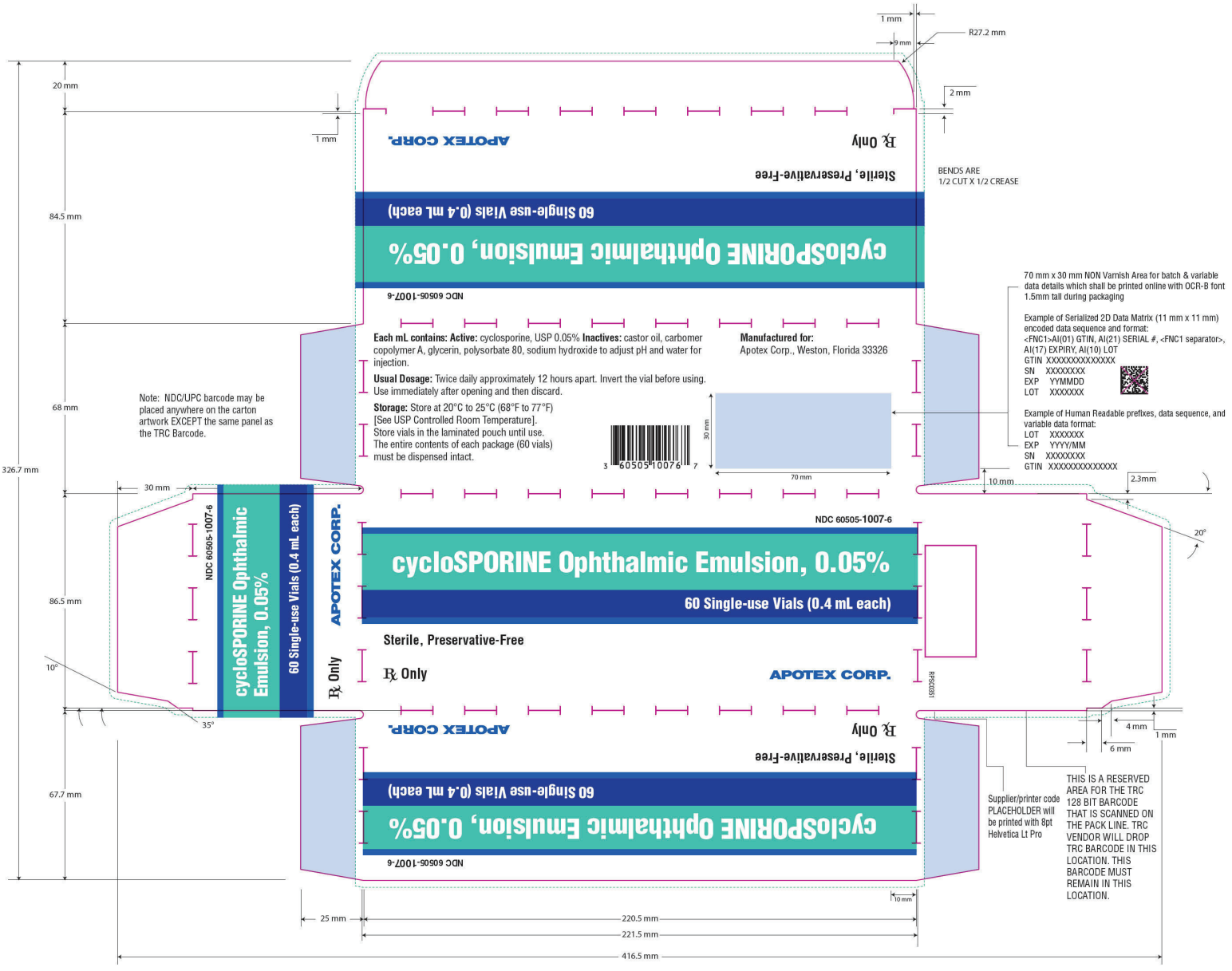
(b) (4)



70 mm x 30 mm NON Varnish Area for batch & variable data details which shall be printed online with OCR-B font 1.5mm tall during packaging

Example of Serialized 2D Data Matrix (11 mm x 11 mm) encoded data sequence and format:
<FNC1>AI(01) GTIN, AI(21) SERIAL #, <FNC1 separator>, AI(17) EXPIRY, AI(10) LOT
GTIN XXXXXXXXXXXXX
SN XXXXXXXX
EXP YYMMDD
LOT XXXXXXX

Example of Human Readable prefixes, data sequence, and variable data format:
LOT XXXXXXX
EXP YYYY/MM
SN XXXXXXXX
GTIN XXXXXXXXXXXXX


1 mm
9 mm
R27.2 mm
2 mm
20 mm
1 mm
APOTEX CORP.
℞ Only
Sterile, Preservative-Free
60 Single-use Vials (0.4 mL each)
cycloSPORINE Ophthalmic Emulsion, 0.05%
NDC 60505-1007-6
BENDS ARE
1/2 CUT X 1/2 CREASE
84.5 mm
70 mm x 30 mm NON Varnish Area for batch & variable data details which shall be printed online with OCR-B font 1.5mm tall during packaging
Example of Serialized 2D Data Matrix (11 mm x 11 mm) encoded data sequence and format: <FNC1>AI(01) GTIN, AI(21) SERIAL #, <FNC1 separator>, AI(17) EXPIRY, AI(10) LOT
GTIN XXXXXXXXXXXXX
SN XXXXXXXX
EXP YYMMDD
LOT XXXXXXX
Each mL contains: Active: cyclosporine, USP 0.05% Inactives: castor oil, carbomer copolymer A, glycerin, polysorbate 80, sodium hydroxide to adjust pH and water for injection.
Manufactured for:
Apotex Corp., Weston, Florida 33326
Usual Dosage: Twice daily approximately 12 hours apart. Invert the vial before using. Use immediately after opening and then discard.
Storage: Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. Store vials in the laminated pouch until use. The entire contents of each package (60 vials) must be dispensed intact.
Note: NDC/UPC barcode may be placed anywhere on the carton artwork EXCEPT the same panel as the TRC Barcode.
3 60505 10076 7
30 mm
70 mm
Example of Human Readable prefixes, data sequence, and variable data format:
LOT XXXXXXX
EXP YYYY/MM
SN XXXXXXXX
GTIN XXXXXXXXXXXXX
68 mm
326.7 mm
30 mm
10 mm
2.3mm
20°
86.5 mm
10°
35°
4 mm
1 mm
6 mm
67.7 mm
Supplier/printer code PLACEHOLDER will be printed with 8pt Helvetica Lt Pro
THIS IS A RESERVED AREA FOR THE TRC 128 BIT BARCODE THAT IS SCANNED ON THE PACK LINE. TRC VENDOR WILL DROP TRC BARCODE IN THIS LOCATION. THIS BARCODE MUST REMAIN IN THIS LOCATION.
25 mm
220.5 mm
221.5 mm
416.5 mm

HIGHLIGHTS OF PRESCRIBING INFORMATION
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.

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 Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2022

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 ophthalmic 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 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

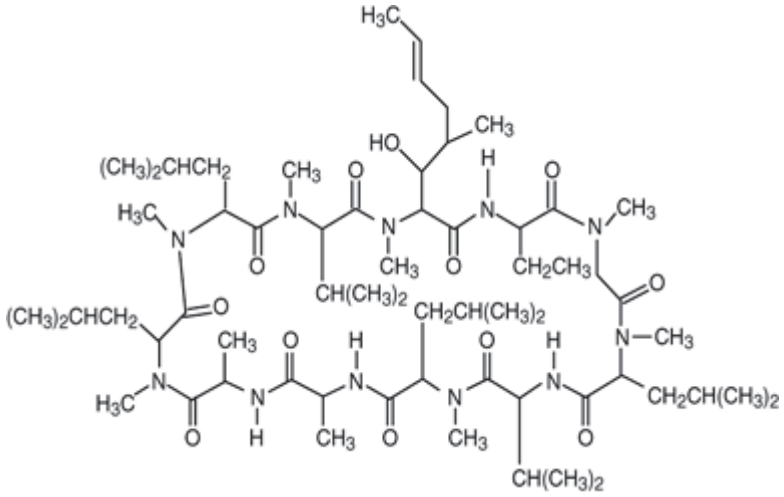
Safety and efficacy have not been established in pediatric patients below the age of 16.

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 immunomodulator with anti-inflammatory effects. Cyclosporine's chemical name is 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 g/mol.

Cyclosporine, USP is a fine white powder. Cyclosporine ophthalmic emulsion appears as white emulsion free from visible particles of foreign matter. 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:** castor oil, carbomer copolymer A, glycerin, polysorbate 80, sodium hydroxide to adjust pH and water for injection.

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 is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.5 mL LDPE vial; five such single use vials are presented in a card and one card is packed in a laminated pouch.

30 Vials 0.4 mL each - NDC 60505-1007-3

6 pouches each pouch containing 1 vial card of 5 single use vials

60 Vials 0.4 mL each - NDC 60505-1007-6

12 pouches each pouch containing 1 vial card of 5 single use vials

Storage: Store at 20ºC to 25ºC (68ºF to 77ºF). [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.

APOTEX CORP.
Cyclosporine Ophthalmic Emulsion
0.05%

Manufactured by:
The Ritedose Corporation
Columbia,
SC 29203, USA.

Manufactured for:
Apotex Corp.
Weston, Florida
33326

Revised: June 2022
Rev. 3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207606Orig1s000

LABELING REVIEW(s)

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	8/9/2022
ANDA Number(s)	207606
Review Number	4
Applicant Name	Apotex Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	NA
Submission Received Date	7/12/2022
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Refer to signature page

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

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

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 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

The Division of Labeling has no further questions/comments at this time based on your labeling submission received July 12, 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, 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

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

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:

The below comments are from the labeling review C1 based on the submission dated 6/18/2014 and 7/7/2015.

1. GENERAL
   a. Per your submission in Section 3.2.P.7, five single use vials are presented in a card which in turn is packed in one laminated pouch. This does not match your insert labeling which states the [redacted] (b) (4) Please verify the number of vials packed in each pouch.
   b. Please verify if the proposed vial labels will be printed on a sticker and attached to the vials, or embossed directly on the vials. If it is to be embossed, please submit photos of the vials with embossing. Alternatively, you may submit samples of the empty embossed vials, without the drug product.

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 (30 Single-use Vials)
   a. See applicable container label comments.
   b. Pouch and carton labeling submitted for review should reflect the content as well as an accurate representation of the layout, color, text size, and style.
   c. Revise the net quantity statement to read as follows, "30 Single-use Vials (0.4 mL each)"
   d. Add a linear bar code to the label per 21 CFR 201.25(c).
   e. Revise "Manufactured By" statement to include country of origin.
   f. 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]."
   g. Revise dispensing statement to read as follows, "….each package(30 vials) must be dispensed intact"

4. POUCH LABELING (60 Single-use Vials)
   a. See applicable container label and Pouch labeling (30 Single-use Vials) comments.
   b. Revise the net quantity statement to read as follows, "60 Single-use Vials (0.4 mL each)
   c. Revise dispensing statement to read as follows, "….each package(60 vials) must be dispensed intact"

5. 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. HOW SUPPLIED: Revise to include the number of vial cards that are packaged in each pouch.

6. STRUCTURED PRODUCT LABELING (SPL)
   a. We acknowledge your commitment to submit the SPL during the review process or within 14 days after the approval of this ANDA.

The below comments are from the labeling review C2 based on the submission dated 3/12/2019.

1. GENERAL COMMENTS
   Please clarify if your final product can be dispensed as one pouch (5 single use vials). If it can only be dispensed as entire carton containing either 30 or 60 vials, please delete (b) (4) statement on pouch and revise the statement in the How Supplied section of prescribing information accordingly.

2. VIAL LABEL
   Revise the established name to include "Tall Man" lettering to be the same as pouch and carton labeling.

3. POUCH LABELING
   See general comment.

4. PRESCRIBING INFORMATION
   See general comment.

In addition, the following deficiency was issued by DP assessor.

The description section of the proposed package insert provides list of inactive ingredients which includes (b) (4) Carbomer copolymer A, please revise the package insert to reflect the change.

Applicant addressed all the above comments. Per applicant, the product can only be dispensed as an entire carton containing either 30 or 60 vials.

Labeling was found to be acceptable in C3 review (6/24/2021 submission). However, a CR letter was issued by chemistry on 5/27/2022 with the following labeling deficiency

We acknowledge that you have revised the package insert, pouch and carton labels to replace (b) (4) Carbomer copolymer A". However, it is noted that the name of this inactive ingredient contains a typographical error as ("Carbonate Copolymer A" instead of "Carbomer Copolymer A"). Please correct the typo.

This amendment provides for revised labeling to correct the inactive ingredient name to appear as "Carbomer

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: Pouch and carton labeling 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:
From quality review finalized 7/28/2020

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

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

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

Reviewer's Note:
Description section provides list of inactive ingredients which still includes [redacted] instead of carbomer copolymer A. We will ask the firm.

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

The description section of the proposed package insert provides list of inactive ingredients (b) (4) Since you have replaced (b) (4) with Carbomer copolymer A, ~~we suggest you~~ revise the package insert to reflect the change.

Labeling deficiency from chemistry review (finalized 3/10/2022)

Firm stated that they have revised the package insert (b) (4), with "Carbomer copolymer A". Firm also mentioned that they have also made the same change on the list of inactive on the Pouch and Carton labeling. Though the firm (b) (4) from the list of inactive from the package insert (Prescribing Information), pouch and carton label, it is noted that the name of this inactive ingredient contains a typographical error as "Carbonate Copolymer A" instead of "Carbomer Copolymer A". We will ask the firm to correct.

Deficiency:
We acknowledge that you have revised the package insert, pouch and carton labels to (b) (4) with "Carbomer copolymer A". However, it is noted that the name of this inactive ingredient contains a typographical error as ("Carbonate Copolymer A" instead of "Carbomer Copolymer A"). Please correct the typo.

DCR clinical review of comparative analyses (finalized 3/21/2022)

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.

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

If Yes, please explain.

Litigation	Internal	Restasis	cyclosporine ophthalmic emulsion; 0.5%	OGD will need to assess certain arguments related to 180-day exclusivity prior to any approval action. OGD continues to consider issues raised in several CPs re approval standards for ANDAs referencing Restasis. Please continue to contact the Policy Lead prior to any communications (CRL, DRL, CC) - or if a new product is filed.

050790	No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence, Filing, Labeling or Quality prior to contacting Policy Lead	No approval actions for this product prior to contacting Policy Lead. Contact Policy prior to issuing either a CRL, or a DRL. No Filing acceptance for applications referencing these products prior to contacting Policy Lead. Reviewers flag this matter for OGDP when they have a recommendation regarding the Q1/Q2 filing assessment stage ANDAs for Cyclosporine Ophthalmic Emulsion, 0.05% (RLD Restasis) are: 203880 (Teva) (b) (4) 205894 (Mylan), 207606 (Apotex), (b) (4) (b) (4) 209811 (Deva Holdings), 211943 (Saptalis) 211943, (b) (4)

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL LABELING

Table 1: Review Model 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): 050790/S-027

Supplement Approval Date: 7/18/2017

Proprietary Name: RESTASIS®

Established Name: Cyclosporine Ophthalmic Emulsion, 0.05%

Description of Supplement:

Please refer to your Supplemental New Drug Application (sNDA) dated February 17, 2017, received February 17, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RESTASIS (cyclosporine ophthalmic emulsion) 0.05%. 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): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

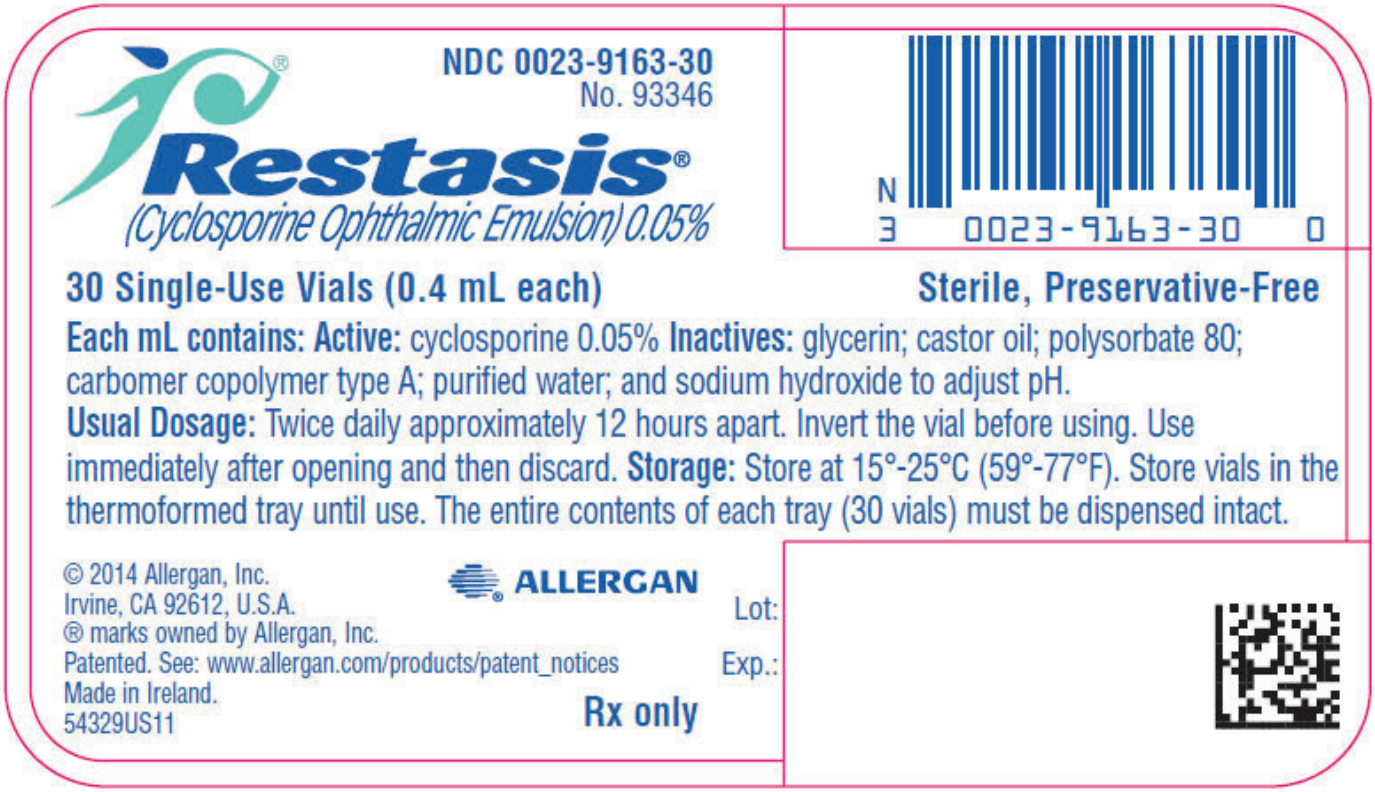
Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: Acceptable

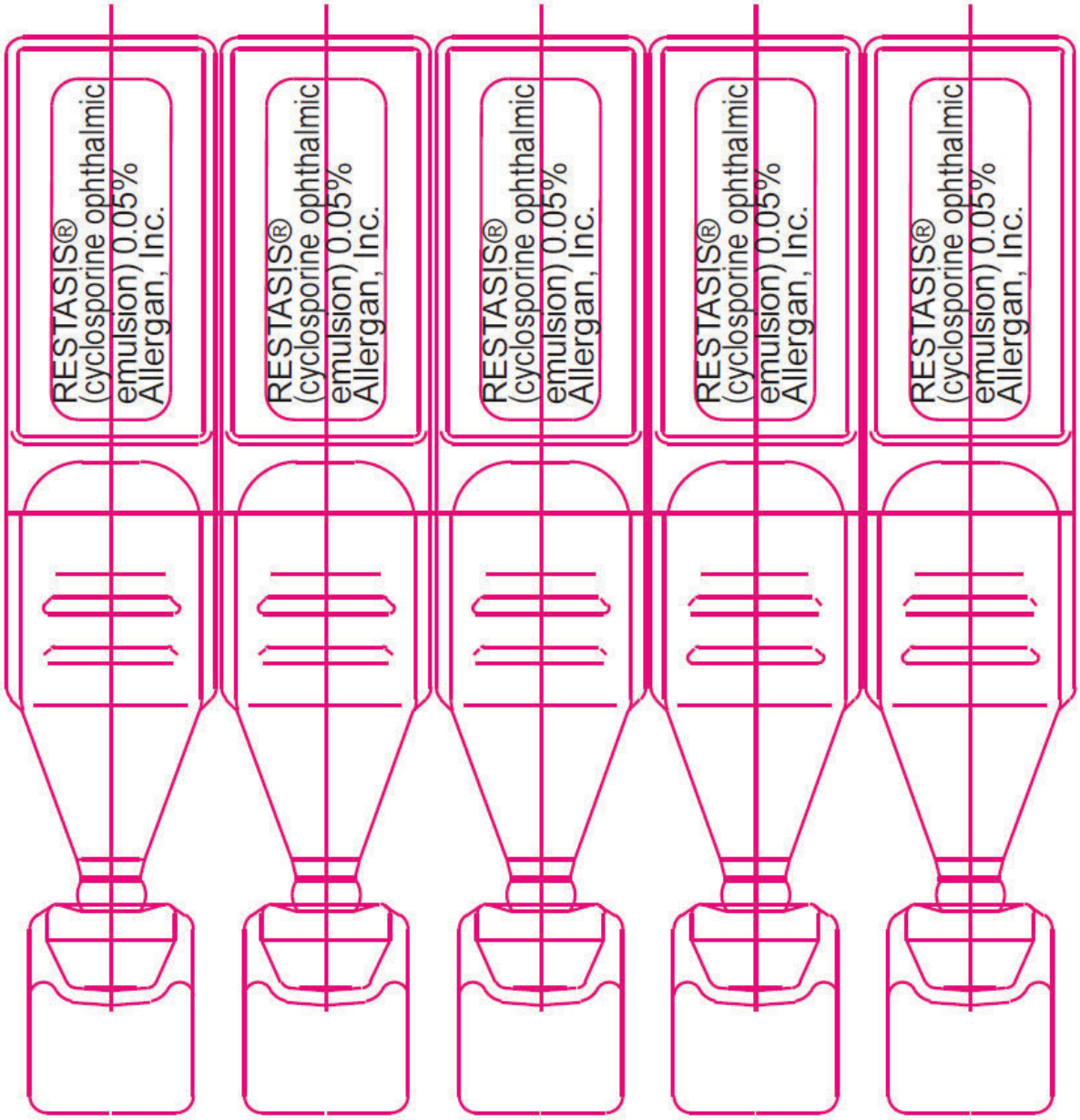
3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-19 received 1/20/2022]

Carton labeling



Vial labeling



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 8/10/2022.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	No		Click here to enter text.	Click here to enter text.
Not Yet Official	Click here to enter text.	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 8/10/2022.

Table 3 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 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)
NA						

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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					

Reviewer Assessment:

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

Reviewer Comments:

Click here 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)? **YES**
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: castor oil, carbonate copolymer A, glycerin, polysorbate 80, sodium hydroxide to adjust pH and water for injection.	IInactives: castor oil, carbomer copolymer A, glycerin, polysorbate 80, sodium hydroxide to adjust pH and water for injection.	carbonate copolymer A was replaced with Carbomer copolymer A as requested by Agency. Change is acceptable.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Cyclosporine ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.5 mL LDPE vial; five such single use vials are presented in a card and one card is packed in a laminated pouch. 30 Vials 0.4 mL each - NDC 60505-1007-3 6 pouches each pouch containing 1 vial card of 5 single use vials 60 Vials 0.4 mL each - NDC 60505-1007-6 12 pouches each pouch containing 1 vial card of 5 single use vials **Storage:** Store at 20ºC to 25ºC (68ºF to 77ºF). [See USP Controlled Room Temperature].	Cyclosporine ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.5 mL LDPE vial; five such single use vials are presented in a card and one card is packed in a laminated pouch. 30 Vials 0.4 mL each - NDC 60505-1007-3 6 pouches each pouch containing 1 vial card of 5 single use vials 60 Vials 0.4 mL each - NDC 60505-1007-6 12 pouches each pouch containing 1 vial card of 5 single use vials **Storage:** Store at 20ºC to 25ºC (68ºF to 77ºF). [See USP Controlled Room Temperature].	No changes

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: The Ritedose Corporation South Carolina, (SC), 29203, USA Manufactured for: Apotex Corp. Weston, Florida 33326	Manufactured by: The Ritedose Corporation Columbia SC 29203, USA Manufactured for: Apotex Corp. Weston, Florida 33326	Minor editorial change

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

6. 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 (Pouch)	Final	5 vials	6/24/2021	Satisfactory
Blister (Vial)	Draft	1 vial	7/12/2022	Satisfactory
Carton	Final	6 pouches each pouch containing 1 vial card of 5 single use vials OR 12 pouches each pouch containing 1 vial card of 5 single use vials	7/12/2022	Satisfactory
(Other – specify)	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
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	Draft	June 2022	7/12/2022	Satisfactory
Medication Guide	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements				

Rita Lindie

Digitally signed by Rita Lindie
Date: 8/10/2022 11:14:48AM
GUID: 53c570830001639fca7572eedfad43b0

Burhan Nour

Digitally signed by Burhan Nour
Date: 8/24/2022 12:14:34PM
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	01/04/2022
ANDA Number(s)	207606
Review Number	3 (Addendum)
Applicant Name	Apotex Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	NA
Submission Received Date	6/24/2021
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Refer to signature page

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

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

-Addendum (01/04/2022): See Section 4 and Section 6

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

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 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

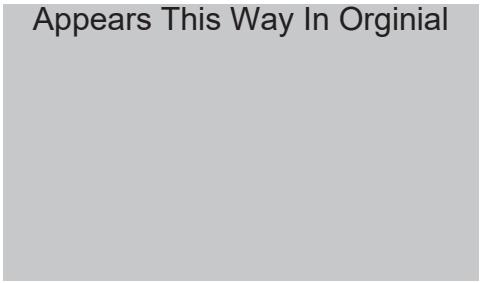
The Division of Labeling has no further questions/comments at this time based on your labeling submission received June 24, 2021.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, 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

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


Appears This Way In Orginial

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:

The below comments are from the labeling review C1 based on the submission dated 6/18/2014 and 7/7/2015.

1. GENERAL
   a. Per your submission in Section 3.2.P.7, five single use vials are presented in a card which in turn is packed in one laminated pouch. This does not match your insert labeling which states the [redacted] (b) (4) Please verify the number of vials packed in each pouch.
   b. Please verify if the proposed vial labels will be printed on a sticker and attached to the vials, or embossed directly on the vials. If it is to be embossed, please submit photos of the vials with embossing. Alternatively, you may submit samples of the empty embossed vials, without the drug product.

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 (30 Single-use Vials)
   a. See applicable container label comments.
   b. Pouch and carton labeling submitted for review should reflect the content as well as an accurate representation of the layout, color, text size, and style.
   c. Revise the net quantity statement to read as follows, "30 Single-use Vials (0.4 mL each)"
   d. Add a linear bar code to the label per 21 CFR 201.25(c).
   e. Revise "Manufactured By" statement to include country of origin.
   f. 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]."
   g. Revise dispensing statement to read as follows, "….each package(30 vials) must be dispensed intact"

4. POUCH LABELING (60 Single-use Vials)
   a. See applicable container label and Pouch labeling (30 Single-use Vials) comments.
   b. Revise the net quantity statement to read as follows, "60 Single-use Vials (0.4 mL each)
   c. Revise dispensing statement to read as follows, "….each package(60 vials) must be dispensed intact"

5. 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. HOW SUPPLIED: Revise to include the number of vial cards that are packaged in each pouch.

6. STRUCTURED PRODUCT LABELING (SPL)
   a. We acknowledge your commitment to submit the SPL during the review process or within 14 days after the approval of this ANDA.

The below comments are from the labeling review C2 based on the submission dated 3/12/2019.

1. GENERAL COMMENTS
   Please clarify if your final product can be dispensed as one pouch (5 single use vials). If it can only be dispensed as entire carton containing either 30 or 60 vials, please delete (b) (4) statement on pouch and revise the statement in the How Supplied section of prescribing information accordingly.

2. VIAL LABEL
   Revise the established name to include "Tall Man" lettering to be the same as pouch and carton labeling.

3. POUCH LABELING
   See general comment.

4. PRESCRIBING INFORMATION
   See general comment.

In addition, the following deficiency was issued by DP assessor.

The description section of the proposed package insert provides list of inactive ingredients which includes (b) (4) (b) (4) Carbomer copolymer A, please revise the package insert to reflect the change.

Applicant addressed all the above comments. Per applicant, the product can only be dispensed as an entire carton containing either 30 or 60 vials.

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: Applicant revised vial, pouch and carton labeling 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:
From quality review finalized 7/28/2020

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

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

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

Reviewer's Note:
Description section provides list of inactive ingredients which still includes (b) (4) instead of carbomer copolymer A. We will ask the firm.

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

The description section of the proposed package insert provides list of inactive ingredients (b) (4) Since you have replaced (b) (4) with Carbomer copolymer A, ~~we suggest you~~ revise the package insert to reflect the change.

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: Labeling reviewer (Rita Lindie) sent an issue on 03/04/2016 regarding Secondary Packaging as follows: (b) (4) (b) (4) Please confirm (b) (4) packaging (laminated pouch) for this ANDA". A response was sent on 05/13/2016 to Rita Lindie as follows: "The ANDA applicant used (b) (4) laminated pouch for (b) (4) packaging,

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CHEMISTRY REVIEW

(b) (4)

(b) (4) Hence, the secondary packaging (laminated pouch) used in ANDA207606 is acceptable.

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

If Yes, please explain.

Litigation	Internal	Restasis	cyclosporine ophthalmic emulsion; 0.5%	OGD will need to assess certain arguments related to 180-day exclusivity prior to any approval action. OGD continues to consider issues raised in several CPs re approval standards for ANDAs referencing Restasis. Please continue to contact the Policy Lead prior to any communications (CRL, DRL, CC) - or if a new product is filed.

050790	No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence, Filing, Labeling or Quality prior to contacting Policy Lead	No approval actions for this product prior to contacting Policy Lead. Contact Policy prior to issuing either a CRL, or a DRL. No Filing acceptance for applications referencing these products prior to contacting Policy Lead. Reviewers flag this matter for OGDP when they have a recommendation regarding the Q1/Q2 filing assessment stage ANDAs for Cyclosporine Ophthalmic Emulsion, 0.05% (RLD Restasis) are: 203880 (Teva) (b) (4) 205894 (Mylan), 207606 (Apotex), (b) (4) (b) (4) 209811 (Deva Holdings), 211943 (Saptalis) 211943, (b) (4)

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL LABELING

Table 1: Review Model 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): 050790/S-027

Supplement Approval Date: 7/18/2017

Proprietary Name: RESTASIS®

Established Name: Cyclosporine Ophthalmic Emulsion, 0.05%

Description of Supplement:

Please refer to your Supplemental New Drug Application (sNDA) dated February 17, 2017, received February 17, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RESTASIS (cyclosporine ophthalmic emulsion) 0.05%. 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): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

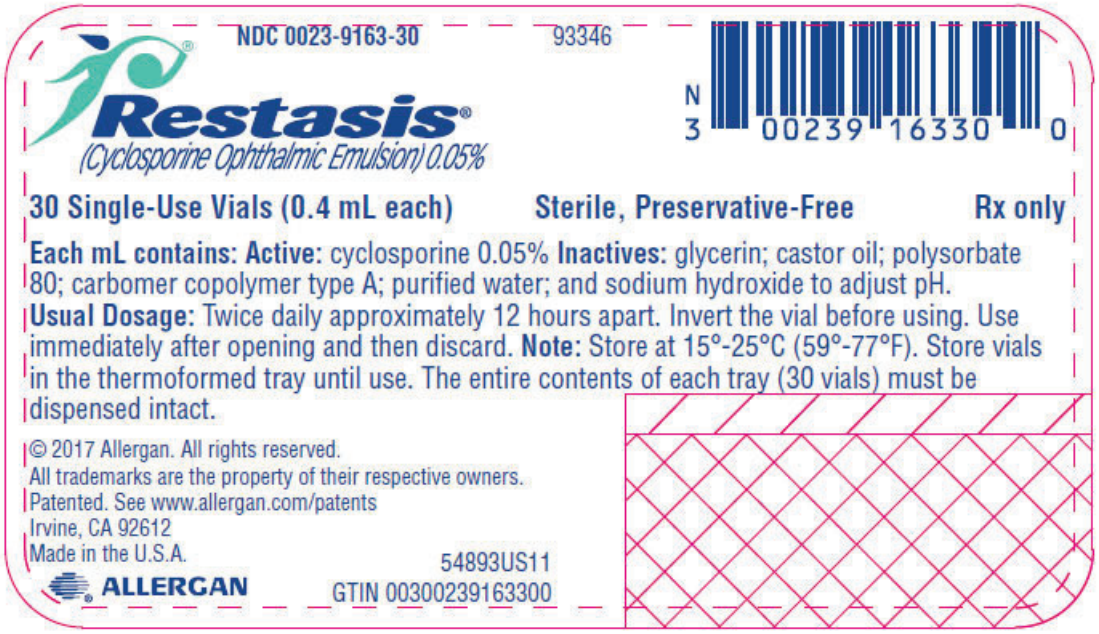
Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: Acceptable

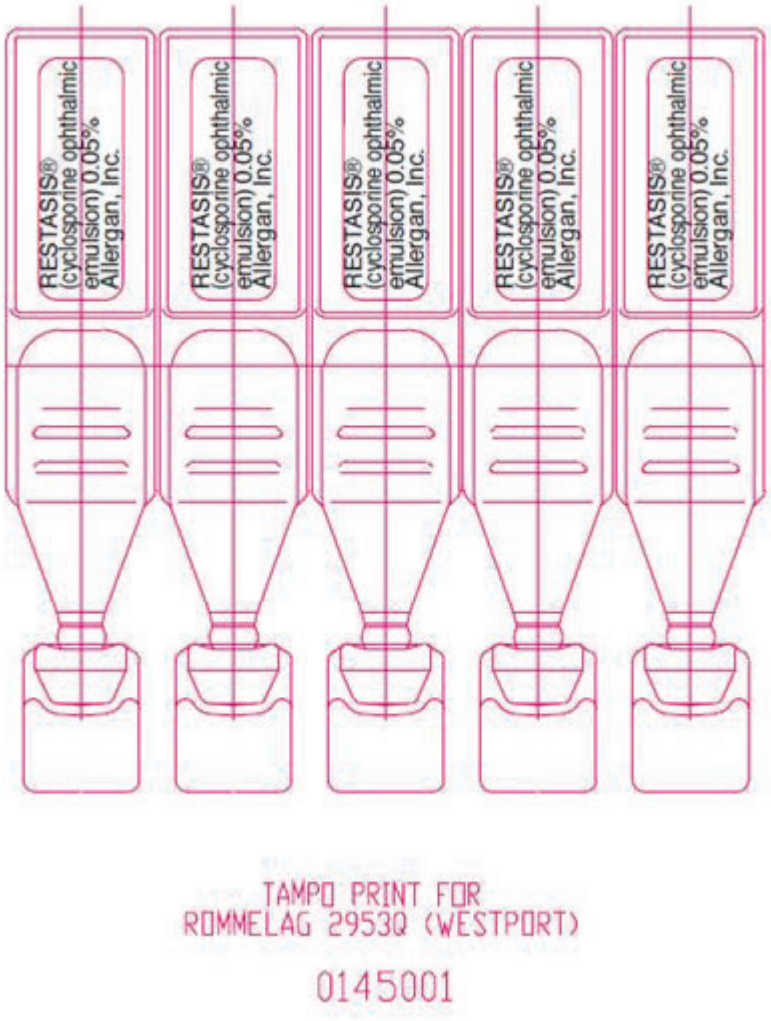
3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-15 received 1/29/2018 & ANRTP-11 received 2/11/2014]

Carton labeling



Vial labeling



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 12/14/2021.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	No		Click here to enter text.	Click here to enter text.
Not Yet Official	Click here to enter text.	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 12/14/2021.

Table 3 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 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	6/18/2014	None
8633162	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	6/18/2014	None
8642556	Aug 27, 2024			PIV	6/18/2014	None
8648048	Aug 27, 2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	6/18/2014	None
8685930	Aug 27, 2024			PIV	6/18/2014	None
9248191	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	2/12/2016	None

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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)
N/A					

Reviewer Assessment:

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

Reviewer Comments:

Click here 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)? **YES**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
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: castor oil, carbonate 1342, glycerin, polysorbate 80, sodium hydroxide to adjust pH and water for injection.	Inactives: castor oil, carbonate copolymer A, glycerin, polysorbate 80, sodium hydroxide to adjust pH and water for injection.	Carbomer 1342 was replaced with Carbomer copolymer A as requested by Agency. Change is acceptable.

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

Previous Labeling Review	Currently Proposed	Assessment
(b) (4)	Cyclosporine ophthalmic emulsion is packaged in sterile, preservative-free single-use vials. Each vial contains 0.4 mL fill in a 0.5 mL LDPE vial; five such single use vials are presented in a card and one card is packed in a laminated pouch. 30 Vials 0.4 mL each - NDC 60505-1007-3 6 pouches each pouch containing 1 vial card of 5 single use vials 60 Vials 0.4 mL each - NDC 60505-1007-6 12 pouches each pouch containing 1 vial card of 5 single use vials **Storage:** Store at 20ºC to 25ºC (68ºF to 77ºF). [See USP Controlled Room Temperature].	Applicant deleted comment, "The entire contents of each pouch must be dispensed intact." as requested by Agency. Change is acceptable.

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
Manufactured by: The Ritedose Corporation South Carolina, (SC), 29203, USA Manufactured for: Apotex Corp. Weston, Florida 33326	Manufactured by: The Ritedose Corporation South Carolina, (SC), 29203, USA Manufactured for: Apotex Corp. Weston, Florida 33326	No changes

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number

or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

6. 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 (Pouch)	Final	5 vials	6/24/2021	Satisfactory
Blister (Vial)	Draft	1 vial	6/24/2021	Satisfactory
Carton	Final	6 pouches each pouch containing 1 vial card of 5 single use vials OR 12 pouches each pouch containing 1 vial card of 5 single use vials	6/24/2021	Satisfactory
(Other – specify)	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
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	Draft	December 2020	6/24/2021	Satisfactory
Medication Guide	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements				

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	4/16/2019
ANDA Number(s)	207606
Review Number	2
Applicant Name	Apotex Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	NA
Submission Received Date	3/12/2019
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Refer to signature page

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

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on April 17, 2019 based on your submission received March 12, 2019:

1. GENERAL COMMENTS
   Please clarify if your final product can be dispensed as one pouch (5 single use vials). If it can only be dispensed as entire carton containing either 30 or 60 vials, please delete "(b) (4) statement on pouch and revise the statement in the How Supplied section of prescribing information accordingly.

2. VIAL LABEL
   Revise the established name to include "Tall Man" lettering to be the same as pouch and carton labeling.

3. POUCH LABELING
   See general comment.

4. PRESCRIBING INFORMATION
   See general comment.

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 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

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

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 OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

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

The below comments are from the labeling review C1 based on the submission dated 6/18/2014 and 7/7/2015.

1. GENERAL
   a. Per your submission in Section 3.2.P.7, five single use vials are presented in a card which in turn is packed in one laminated pouch. This does not match your insert labeling which states the [redacted] Please verify the number of vials packed in each pouch.
   b. Please verify if the proposed vial labels will be printed on a sticker and attached to the vials, or embossed directly on the vials. If it is to be embossed, please submit photos of the vials with embossing. Alternatively, you may submit samples of the empty embossed vials, without the drug product.

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 (30 Single-use Vials)
   a. See applicable container label comments.
   b. Pouch and carton labeling submitted for review should reflect the content as well as an accurate representation of the layout, color, text size, and style.
   c. Revise the net quantity statement to read as follows, "30 Single-use Vials (0.4 mL each)"
   d. Add a linear bar code to the label per 21 CFR 201.25(c).
   e. Revise "Manufactured By" statement to include country of origin.
   f. 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]."
   g. Revise dispensing statement to read as follows, "….each package(30 vials) must be dispensed intact"

4. POUCH LABELING (60 Single-use Vials)
   a. See applicable container label and Pouch labeling (30 Single-use Vials) comments.
   b. Revise the net quantity statement to read as follows, "60 Single-use Vials (0.4 mL each)
   c. Revise dispensing statement to read as follows, "….each package(60 vials) must be dispensed intact"

5. 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. HOW SUPPLIED: Revise to include the number of vial cards that are packaged in each pouch.

6. STRUCTURED PRODUCT LABELING (SPL)
   a. We acknowledge your commitment to submit the SPL during the review process or within 14 days after the approval of this ANDA.

From response to CRL

Please note that the text on the vial as per the draft label in section 1.14.1.1, will be etched on one side of the vial (expiry date and lot number) and embosed on the other side (name of the product and manufacturer). Please see **Figure 1** below for photo of the vials displaying the etched side . Due to the high cost of the embossing plates, samples of vials displaying the embossed name and manufacturer as indicated in the draft label in section 1.14.1.1, as well as in the vial card drawing in section 3.2.P.7, are not yet available. The embossing plate will be ordered once the review of the labeling portion is finalized and agreed upon by the Agency.

(b) (4)

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:
Applicant revised vial, pouch and carton labeling as requested. See section 2 above for picture of vial. We noted that Tall Man lettering is not on the draft labeling of the vial. Will ask applicant to revise.

The pouch labeling statement was revised to state, "The entire contents of each package (5 vials) must be dispensed intact" and the carton labeling "The entire contents of each package (30 vials) must be dispensed intact". Will ask applicant to clarify if product can be dispensed as one pouch (5 vials). If not, delete statement on pouch.

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:
From quality review

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

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: NA

Is tamper evident feature provided in the container/closure?

☐ Yes ☐ No

If "No," explain.

e) For solid oral drug products, only: drug product length(s) of commercial batch(es): NA

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:
Labeling reviewer (Rita Lindie) sent an issue on 03/04/2016 regarding (b) (4) (b) (4) (b) (4) packaging (laminated pouch) for this ANDA". A response was sent on 05/13/2016 to Rita Lindie as follows: "The ANDA applicant (b) (4) laminated pouch for (b) (4) packaging,

-100-

CHEMISTRY REVIEW

(b) (4) (b) (4) packaging (laminated pouch) used in ANDA207606 is acceptable.

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

If Yes, please explain.

Litigation	Internal	Restasis	cyclosporine ophthalmic emulsion; 0.5%	On February 26, 2019, the Court granted FDA's motion to dismiss the compliant. It is possible that Teva could appeal the Court's ruling. OGD continues to consider issues raised in several CPs re approval standards for ANDAs referencing Restasis. Please continue to contact the Policy Lead prior to any communications (CRL, DRL, CC) - or if a new product is filed.	050790
No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead		No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence, Filing, Labeling or Quality		No approval actions for this product prior to contacting Policy Lead. Contact Policy prior to issuing either a CRL, or a DRL. No Filing acceptance for applications referencing these products prior to contacting Policy Lead. Reviewers flag this matter for OGDP when they have a recommendation regarding the Q1/Q2 filing assessment stage ANDAs for Cyclosporine Ophthalmic Emulsion, 0.05% (RLD Restasis) are: 203880 (Teva), (b) (4) 205894 (Mylan), 207606 (Apotex), (b) (4) 209811 (Deva Holdings), 211943 (Saptalis) 211943, (b) (4)	10/17/2018

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL LABELING

Table 1: Review Model 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):** 050790/S-027 **Supplement Approval Date:** 7/18/2017 **Proprietary Name:** RESTASIS® **Established Name:** Cyclosporine Ophthalmic Emulsion, 0.05% **Description of Supplement:** Please refer to your Supplemental New Drug Application (sNDA) dated February 17, 2017, received February 17, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RESTASIS (cyclosporine ophthalmic emulsion) 0.05%. 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):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) 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), or 201.66 (OTC)? **CLICK HERE**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

Comment to applicant:

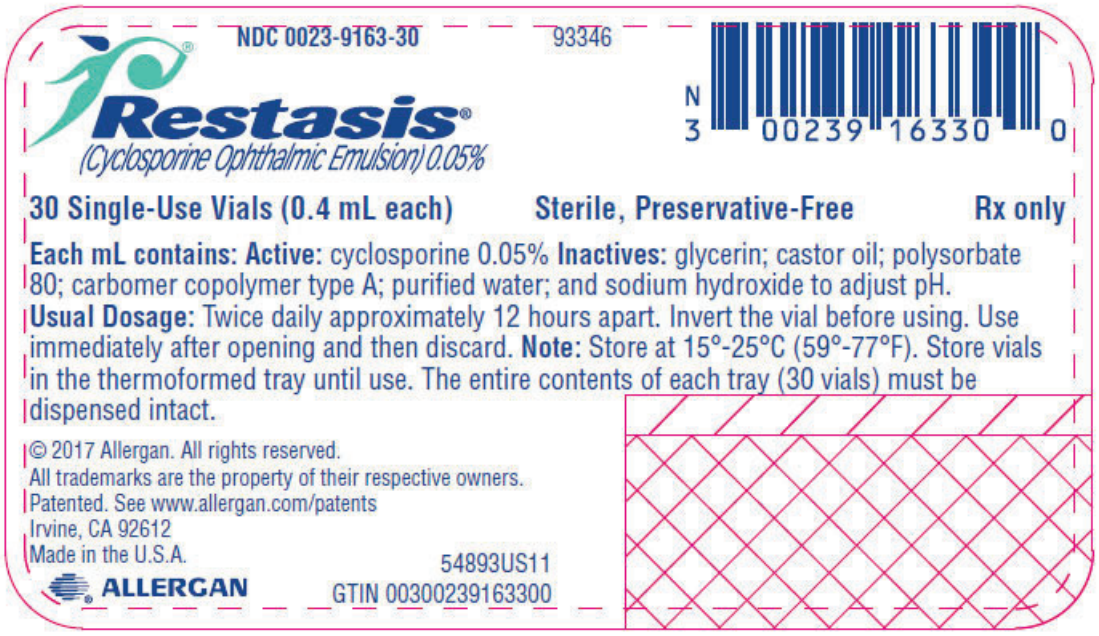
Please clarify if your final product can be dispensed as one pouch (5 single use vials). If it can only be dispensed as entire carton containing either 30 or 60 vials, please delete "(b) (4) (b) (4) statement on pouch and revise the statement in the How Supplied section of prescribing information accordingly.

The SPL was submitted for review. It is acceptable.

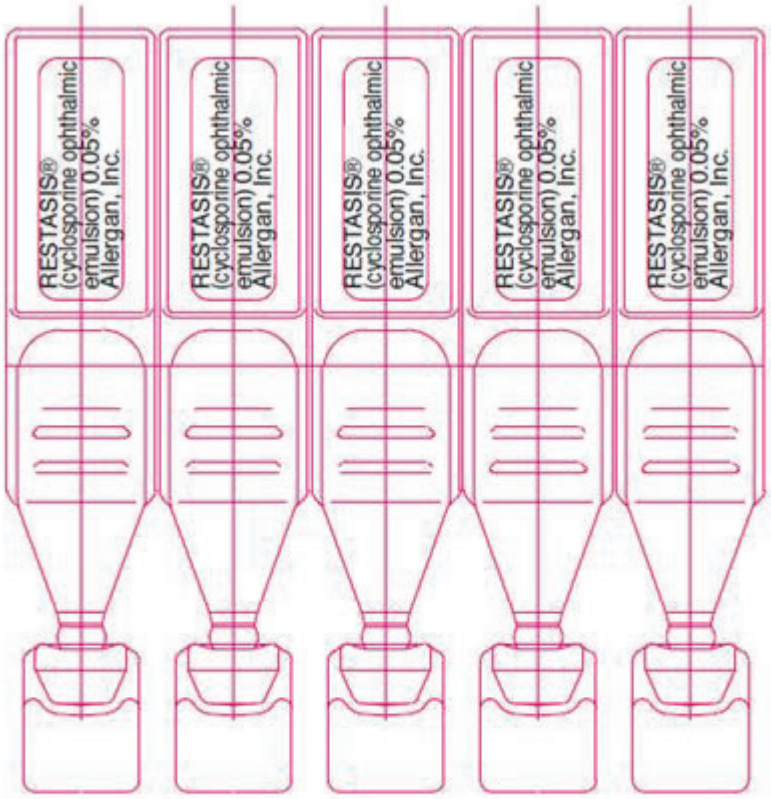
3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-15 received 1/29/2018 & ANRTP-11 received 2/11/2014]

Carton labeling



Vial labeling



TAMPO PRINT FOR
ROMMELAG 2953Q (WESTPORT)

0145001

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 4/16/2019.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	No		Click here to enter text.	Click here to enter text.
Not Yet Official	Click here to enter text.	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/16/2019.

Table 3 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 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	6/18/2014	None
8633162	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	6/18/2014	None
8642556	Aug 27, 2024			PIV	6/18/2014	None
8648048	Aug 27, 2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	6/18/2014	None
8685930	Aug 27, 2024			PIV	6/18/2014	None
9248191	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	2/12/2016	None

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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)**
Click here to enter text.					

Reviewer Assessment:

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

Reviewer Comments:

Click here 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)? **YES**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
Are there changes to the manufacturer/distributor/packer statements? **YES**
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**
(b) (4)		

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)	ee comment in Section 3.2.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)		

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

6. 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 (Pouch)	Final	5 vials	3/12/2019	Revise
Blister (Vial)	Draft	1 vial	3/12/2019	Satisfactory
Carton	Final	6 pouches each pouch containing 1 vial card of 5 single	3/12/2019	Satisfactory

		use vials OR 12 pouches each pouch containing 1 vial card of 5 single use vials		
(Other – specify)	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.

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	Draft	March 2019	3/12/2019	Revise
Medication Guide	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements		3/2019	3/12/2019	Satisfactory

Rita Lindie

Digitally signed by Rita Lindie
Date: 4/19/2019 11:53:58AM
GUID: 53c570830001639fca7572eedfad43b0

Theresa Liu

Digitally signed by Theresa Liu
Date: 4/22/2019 11:31:26AM
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	2/26/2016
ANDA Number(s)	207606
Review Number	1
Applicant Name	Apotex Inc.
Established Name & Strength(s)	Cyclosporine Ophthalmic Emulsion, 0.05%
Proposed Proprietary Name	NA
Submission Received Date	6/18/2014 and 7/7/2015
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

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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 June 18, 2014 and July 7, 2015:

1. GENERAL
    a. Per your submission in Section 3.2.P.7, five single use vials are presented in a card which in turn is packed in one laminated pouch. This does not match your insert labeling which states the "contents of each pouch (30 vials or 60 vials)". Please verify the number of vials packed in each pouch.

    b. Please verify if the proposed vial labels will be printed on a sticker and attached to the vials, or embossed directly on the vials. If it is to be embossed, please submit photos of the vials with embossing. Alternatively, you may submit samples of the empty embossed vials, without the drug product.

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 (30 Single-use Vials)
    a. See applicable container label comments.
    b. Pouch and carton labeling submitted for review should reflect the content as well as an accurate representation of the layout, color, text size, and style.
    c. Revise the net quantity statement to read as follows, "30 Single-use Vials (0.4 mL each)"
    d. Add a linear bar code to the label per 21 CFR 201.25(c).
    e. Revise "Manufactured By" statement to include country of origin.
    f. 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]."
    g. Revise dispensing statement to read as follows, "….each package(30 vials) must be dispensed intact"

4. POUCH LABELING (60 Single-use Vials)
    a. See applicable container label and Pouch labeling (30 Single-use Vials) comments.
    b. Revise the net quantity statement to read as follows, "60 Single-use Vials (0.4 mL each)
    c. Revise dispensing statement to read as follows, "….each package(60 vials) must be dispensed intact"

5. 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. HOW SUPPLIED: Revise to include the number of vial cards that are packaged in each pouch.

6. STRUCTURED PRODUCT LABELING (SPL)
   a. We acknowledge your commitment to submit the SPL during the review process or within 14 days after the approval of this ANDA.

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

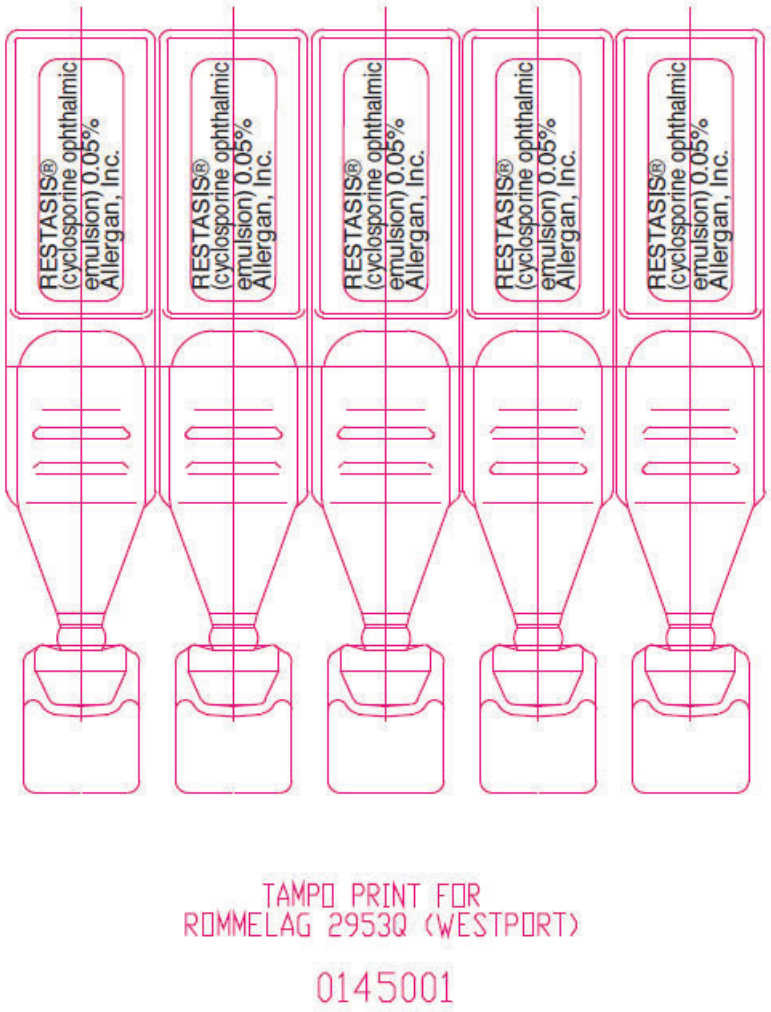
Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if 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.
☐ **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 Labeling

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	2/26/2016	No	NA to enter text.	NA to enter text.
PF	2/26/2016	No	NA to enter text.	NA to enter text.

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/26/2016.

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	6/18/2014	None
8633162	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	6/18/2014	None
8642556	Aug 27, 2024			PIV	6/18/2014	None
8648048	Aug 27, 2024	U-1483	INCREASE TEAR PRODUCTION IN PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	6/18/2014	None
8685930	Aug 27, 2024			PIV	6/18/2014	None
9248191	Aug 27, 2024	U-1479	INCREASE TEAR PRODUCTION TO TREAT PATIENTS WITH KERATOCONJUNCTIVITIS SICCA (DRY EYE).	PIV	2/12/2016	

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					

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

Comments to firm
- 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."

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**
(b) (4)	

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:

B. Composition:

(b) (4)

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? **NO**
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:

- Per your submission in Section 3.2.P.7, five single use vials are presented in a card which in turn is packed in one laminated pouch. This does not match your insert labeling which states the "contents of each pouch (30 vials or 60 vials)". Please verify the number of vials packed in each pouch.
-Revise the "HOW SUPPLIED" Section to include the number of vial cards that are packaged in each pouch.
- 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): **NA**

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

- Please verify if the proposed vial labels will be printed on a sticker and attached to the vials, or embossed directly on the vials. If it is to be embossed, please submit photos of the vials with embossing. Alternatively, you may submit samples of the empty embossed vials, without the drug product.
- 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? **NO**

Reviewer Comments:

Comments to firm
Pouch Label- 30 Single-use Vials
-See applicable container label comments.
- Pouch and carton labeling submitted for review should reflect the content as well as an accurate representation of the layout, color, text size, and style.
-Revise the net quantity statement to read as follows, "30 Single-use Vials (0.4 mL each)
- Add a linear bar code to the label per 21 CFR 201.25(c).
-Revise "Manufactured By" statement to include country of origin.
-Revise dispensing statement to read as follows, "….each package(30 vials) must be dispensed intact"

Pouch Label- 60 Single-use Vials
- See applicable container label and Pouch Labeling (30 Single-use Vial) comments.
- Revise the net quantity statement to read as follows, "60 Single-use Vials (0.4 mL each)
- Revise dispensing statement to read as follows, "….each package(60 vials) must be dispensed intact"

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:

From 3.2.P.7

(b) (4)

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? **NO**
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? **NA**

Reviewer Comments:
From 6/18/2014 submission:

> Apotex is submitting the draft drug product labeling for Cyclosporine ophthalmic emulsion, 0.05 % in this original ANDA submission. However, Apotex commits to provide the content of labeling in SPL format for Cyclosporine Ophthalmic Emulsion 0.05 % in the course of the labeling review process.

Comment to firm:
We acknowledge your commitment to submit the SPL during the review process or within 14 days after the approval of this ANDA.

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 (laminated 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 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

D. Secondary Packaging **ADEQUATE**

(b) (4)

[redacted]

9. STABILITY **INADEQUATE**

(b) (4)

[redacted]

Stability data: vol. 1.4, pgs. 023 to 280 **ADEQUATE**

Amendment dated 5/10/99

(b) (4)

[redacted]

(b) (4)

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	6/18/2014	Revise
Blister	NA	NA to enter text.	NA to enter text.	NA to enter text.
Carton (Pouch)	NA	1 pouch containing 30 vials or 60 vials	6/18/2014	Revise
(Other – specify)	NA	NA to enter text.	NA to enter text.	NA to enter text.
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 2014 Rev. 0	7/7/2015	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	Not Submitted	NA to enter text.	NA to enter text.	NA to enter text.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207606Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Adequate

ANDA:

☒ **Approval**

☐ **Information Request – Minor**

(_____days for applicant to response)

☐ **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 207606
Review # 04a

Amendment Review

Drug Name/Dosage Form	Cyclosporine Ophthalmic Emulsion
Strength	0.05%
Reviewer(s)	Asif Rasheed
Applicant	Apotex Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
eCTD 0026 Response to CR	07/12/2022
eCTD 0027 Response to IR	12/09/2022

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Cyclosporine API	Adequate	12/01/2022	Reviewed by Wei Song
	III		(b) (4)	N/A		
	III			N/A		

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

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

FACILITIES:

(b) (4)

(b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

POST APPROVAL COMMITTMENTS:
None.

Notes: For the Review of the Amendment:

1. Only the sections of 2.3.S and/or 2.3.P that have deficiency responses and/or changes (b) (4) need to be updated. It is unnecessary to keep the QbR questions or information that has been archived in the previous review.

2. If there are no changes to a particular section, write "No Change".

3. For each updated section, include deficiency / comment, **pertinent** data/information from the applicant's response, and the review assessment using the following format:

Assessment of the submission on 7/12/2022 for the responses to CR sent on 5/27/2022

(b) (4)

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Overall Reviewer's Assessment and Signature:
Approvable

Asif Rasheed, 09/18/2022, 12/01/2022, 12/09/2022

Secondary Review Comments and Concurrence:
DMF and DP: adequate

Hongmei Li, 9/20/2022, 12/13/2022

List of Deficiencies to Be Communicated by Information Request or Complete Response:

Drug Substance

None

Drug Product
None

Label/Labeling
None

Asif Rasheed

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Date: 12/13/2022 10:06:10AM
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Hongmei Li

Digitally signed by Hongmei Li
Date: 12/13/2022 09:55:00AM
GUID: 54c94ca000084932f06afe87774bef34

Recommendation:
ANDA:
☐ **Approval**
☐ **Information Request – Minor**
(_____days for applicant to response)
☒ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 207606
Review # 03

Amendment Review

Drug Name/Dosage Form	Cyclosporine Ophthalmic Emulsion
Strength	0.05%
Reviewer(s)	Asif Rasheed
Applicant	Apotex Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
eCTD 0020 Response to CRL	06/24/2021
eCTD 0021 Amendment	04/01/2021
eCTD 0022 Amendment (Response to IR on Drug-Device Combination product)	07/07/2021
eCTD 0023 Amendment (Response to IR on Drug-Device Combination product)	11/01/2021

eCTD 0017 and 0019 include administrative info. eCTD 0018 includes reference to a journal article. eCTD 0024 and 0025 include comparative analysis report

DMFs:

Note any status changes as applicable or if no change, reference last Quality Review ###

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Cyclosporine API	Inadequate	01/14/2022	Reviewed by Wei Song
	III		(b) (4)	N/A		
	III			N/A		

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

Note any status changes as applicable or if no change, reference last Quality Review ###

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

FACILITIES:

(b) (4)

(b) (4) All facilities are deemed acceptable to support this ANDA at this time.

(b) (4)

UPDATED RISK ASSESSMENT:

(b) (4)

[redacted]

(b) (4)

POST APPROVAL COMMITTMENTS:
None.

Notes: For the Review of the Amendment:

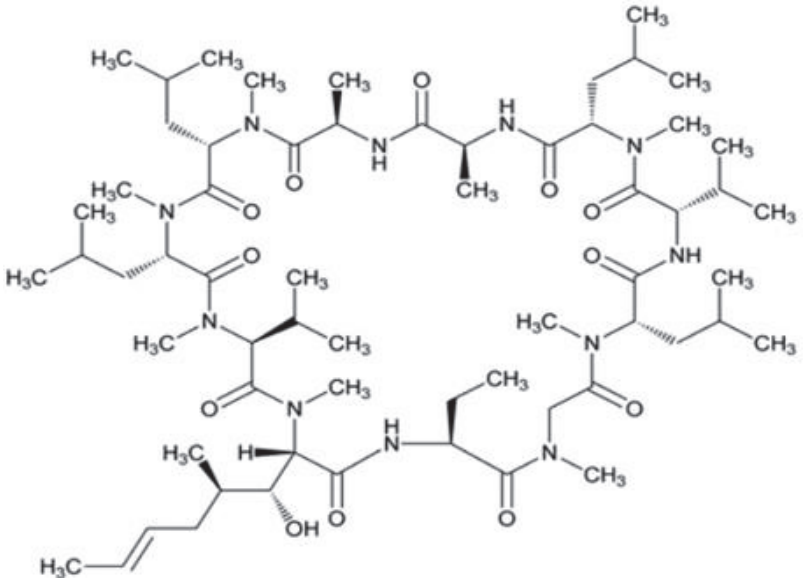
1. Only the sections of 2.3.S and/or 2.3.P that have deficiency responses and/or changes (b) (4)) need to be updated. It is unnecessary to keep the QbR questions or information that has been archived in the previous review.

2. If there are no changes to a particular section, write "No Change".

3. For each updated section, include deficiency / comment, **pertinent** data/information from the applicant's response, and the review assessment using the following format:

Deficiency/Comment #1:
The structural formula provided in Section 3.2.S.1 indicates three hydrogen bonds between the oxygen atom of carbonyl (-CO) groups and hydrogen atom of amine (-NH) groups present within the structure. Please revise the section to include Cyclosporine structure to be consistent with the USP monograph for this drug.

Summary of Applicant's Response:
We acknowledge the agency's comment and have revised section 3.2.S.1.2 to include the Cyclosporine structure below, in order to be consistent with the USP monograph for this drug.



Reviewer's Assessment: Acceptable

Firm has revised the structural formula for cyclosporine to be consistent with that of the USP monograph. The revised structural formula has been updated in Section

3.2.S.1 as well as in the drug product package insert (prescribing information in Section 1.14.2.3). Firm's response is acceptable.

–

Deficiency/Comment #2:
We acknowledge the information you provided in module 3.2.S.1, which indicate that the drug substance is freely soluble in methanol, ethanol, methylene chloride, acetone, chloroform, water, and saturated hydrocarbons, and is also soluble in ether. (b) (4)

(b) (4)

Summary of Applicant's Response:
We have consulted with the DMF holder and have revised section 3.2.S.1.3, as per below, to be consistent with the information on drug substance solubility provided in DMF # (b) (4)

Reviewer's Assessment: Acceptable

Firm has revised Section 3.2.S.1.3 for solubility information for the drug substance to be consistent with that of the DMF (b) (4) Firm has also provided information on

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Asif Rasheed

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Hongmei Li

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Date: 3/10/2022 09:04:24AM
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U.S. FOOD & DRUG ADMINISTRATION

ANDA Status: Not Approvable – Inadequate, CR - Minor

ANDA 207606
Cyclosporine Ophthalmic Emulsion, 0.05%
Apotex Inc.

Addendum to the Drug Product Review Dated 07/16/2020 (Assessment 2a)

CHAPTER I: DRUG SUBSTANCE

IQA ANDA Assessment Guide Reference

Please see review dated 07/16/2020 for assessment on Drug Substance sections

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Product Information	
ANDA Number	207606
Assessment Cycle Number	2a
Drug Product (DP) Name / Strength	Cyclosporine Ophthalmic Emulsion, 0.05%
Route of Administration	Ophthalmic
Drug Product Manufacturer	Apotex Inc. (Manufacturing facility – The Ritedose Corporation, TRC)
RLD/RS Information (Brand Name of Product, Applicant)	Restasis by Allergan, Inc
RLD/RS Number	NDA 050790
Proposed Indication	Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

Assessment Recommendation: N/A (please see drug product review dated 07/16/2020 for details on assessment and recommendation).

P.1 DESCRIPTION AND COMPOSITION

This Addendum is intended to revise the calculations for the Q2 assessment of (b) (4) used in the Drug Product Quality Assessment document dated July 16, 2020. Specifically, this addendum addresses the value used for calculating the amount of (b) (4) in the reference listed drug (RLD). The revised calculations do not alter the conclusion that the proposed product is Q2 the same as the RLD with respect to (b) (4)

(b) (4)

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Asif Rasheed

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Norman Ohler

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Date: 12/14/2020 06:44:32AM
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U.S. FOOD & DRUG ADMINISTRATION

[1]ANDA Status: Not Approvable – Inadequate, CR - Minor

ANDA 207606
Assessment 2a
Cyclosporine Ophthalmic Emulsion, 0.05%
Apotex Inc.

QUALITY ASSESSMENT DATA SHEET

IQA ANDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Cyclosporine API	Adequate	10/26/2018	by Siba Bhattacharya
	III		(b) (4)	Adequate info within ANDA		
	III			Adequate info within ANDA		
	Other					

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved ANDA*

[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.

Document	Application Number	
NDA	50790	Restasis

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other (OPQ/OTR)	Complete	Deficiencies for GSD method and validation	06/11/2019	Xiaoming Xu

CHAPTER I: DRUG SUBSTANCE

IQA ANDA Assessment Guide Reference

Drug Substance Name	Cyclosporine
ANDA Number	207606
Applicant Name	Apotex
Assessment Cycle Number	2a
DMF Number (If Applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: **Inadequate - Minor**

Theme:

Assessment Summary:

Cyclosporine ophthalmic emulsion 0.05% contains a topical immunomodulator with anti-inflammatory effects. (b) (4) It is a white to almost white powder. Its molecular weight is 1202.6 g/mol. Practically insoluble in water, Soluble in acetone, in methanol, in ethanol, in chloroform, and in methylene chloride. The drug substance does not exhibit polymorphism. Chemically, cyclosporine is a stable compound. Cyclosporine is official in the USP. The specifications and acceptance criteria conform to USP monograph requirements. (b) (4) This DMF is adequate.

List Submissions being assessed (*Table*):

eCTD 0016 07/16/2019, Response to BE regarding amount of NaOH

eCTD 0012, 0013, 0014 contains administrative information.

Highlight Key Issues from Last Cycle and Their Resolution:

Concise Description of Outstanding Issues (*List bullet points with key information and update as needed*):

Select Number of Approved Comparability Protocols: 0

Part I – Review of CRL Responses:

(b) (4)

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Primary Drug Product Assessor Name and Date: Asif Rasheed, 08/05/2019, 11/16/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed): Chandan M Thomas, 08/07/2019; Norman E Ohler, 11/18/2019

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

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

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

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

Reviewer's Note:
Description section provides list of inactive ingredients which still includes carbomer 1342 instead of carbomer copolymer A. We will ask the firm.

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

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:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No ☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

The description section of the proposed package insert provides list of inactive ingredients (b) (4) with Carbomer copolymer A, revise the package insert to reflect the change.

Primary Drug Product Assessor Name and Date: Asif Rasheed, 08/05/2019, 11/16/2019

Secondary Drug Product Assessor Name and Date: Chandan M Thomas, 08/07/2019; Norman E Ohler, 11/18/2019

Asif Rasheed

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Date: 7/16/2020 04:11:42PM
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Norman Ohler

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Date: 7/16/2020 03:52:39PM
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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 due to CMC Minor Deficiencies***

ANDA 207606

Cyclosporine Ophthalmic Emulsion 0.05%

Apotex Inc.

Sri Rama Krishnaiah, Yellela Ph.D.

Division of Product Quality Research
Office of Testing and Research

Table of Contents

Chemistry Review Data Sheet

1. **ANDA#** : **207606**
2. **REVIEW #** : **1b**
3. **REVIEW DATE** : **08/23/2015; 12/22/2015*; 10/20/2016**
4. **REVIEWER** : **Sri Rama Krishnaiah, Yellela, Ph.D.**
   : ***Xiaoming Xu, Ph.D. (12/22/2015)**
5. **PREVIOUS DOCUMENTS** :

Previous Document(s)	Document Date
None	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original Submission (Original-1)	06/18/2014
Quality/ Response to Information Request	07/07/2015
Quality/Response to Information Request	07/08/2015
Patent & Exclusivity/ Patent Certification	07/29/2015
Patent & Exclusivity/ Patent Certification	08/26/2015
Correspondence (regarding samples)	10/21/2015
Correspondence (regarding samples)	01/20/2016
Patent Amendment/P-IV certification for newly listed patent	02/12/2016
Patent Amendment/Proof of Receipt of Notice to Patent Holders	02/26/2016
Quality/Response to Information Request	03/18/2016
Quality/Response to Information Request (Tamper Evidence)	03/24/2016
Patent Amendment/Notice of Non-Litigation	04/04/2016
Quality/Response to Information Request (Microbiology)	08/30/2016

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Apotex Inc.
Address:	150 Signet Drive Toronto, Ontario State Canada
Representative:	Kiran Krishnan Vice President, US Regulatory Affairs Apotex Corp 2400 North Commerce Parkway, Suite 400 Weston, FL 33326
Telephone:	954-384-3986

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Chemistry Review Data Sheet

Proprietary Name:	None
Non-Proprietary Name (USAN):	Cyclosporine Ophthalmic Emulsion 0.05%

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product:	Restasis® Ophthalmic Emulsion (Cyclosporine Ophthalmic Emulsion, 0.05%)			
Innovator Company:	Allergan Inc. (NDA 050790, approval date: 12/23/2002)			
Patent Data:	As on 05/10/2016, there are 6 patents listed in the Orange Book as being relevant to this application. Generic sponsor has provided Paragraph IV Certification for all 6 patents. The sponsor has provided Paragraph II certification in respect of the patent "5474979" which expired on May 17, 2014. The RLD has two of the patient use codes U-1479 and U-1483 (Increase tear production to treat patients with Keratoconjuctivitis Sicca [Dry Eye]).			
	Patent No	**Expiry Date**	**Certification**	**Date of Submission**
	8629111	August 27, 2024	P-IV	02/27/2014
	8633162	August 27, 2024	P-IV	02/27/2014
	8642556	August 27, 2024	P-IV	02/27/2014
	8648048	August 27, 2024	P-IV	02/27/2014
	8685930	August 27, 2024	P-IV	02/27/2014
	9248191	August 27, 2024	P-IV	02/12/2016
Exclusivity Data:	Firm has certified that there is no unexpired exclusivity for RLD.			

10. PHARMACOLOGICAL CATEGORY: Ophthalmic- Immune System Regulator

11. DOSAGE FORM: **Ophthalmic Emulsion**

12. STRENGTH/POTENCY: **0.05%**

13. ROUTE OF ADMINISTRATION: **Ophthalmic**

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

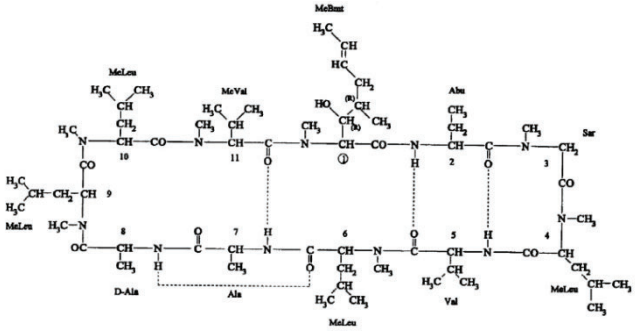
☒ Not a NANO product

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
Molecular Formula	$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight	1202.6 g/mol
CAS number	59865-13-3
Nomenclature:	Cyclo[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octanoyl]-L-2-aminobutyryl-Nmethylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-Nmethyl-L-valyl
Molecular Structure	

Abbreviation Key	
Sar	Sarcosine
Ala	Alanine
MeLeu	Methyl leucine
Val	Valine
MeBmt	(2S,3R,4R,6E) -2-methylamino-3-hydroxy-4-methyl-oct-6-enoic acid
MeVal	Methyl valine
Abu	Amino butyric acid

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLE-TED
(b) (4)	II	(b) (4)	Cyclosporine USP	1	**Adequate**	Jizhou Wang, dated 10/19/2016
	III		(b) (4)	4	NA	NA
	III			4	NA	NA

[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 050790	RLD Product

18. STATUS

CONSULTS/CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		**Adequate**	9/2/2016	Denise Miller
Methods Validation		N/A		
Labeling		**Inadequate**	03/04/2016	Rita Lindie
Bioequivalence	Dissolution (In vitro drug release test)	**Inadequate**	10/4/2016	Patrick Nwakama
	Bioequivalence (In vitro quality metrics)	**Inadequate**	10/4/2016	Patrick Nwakama
Toxicology/Clinical		N/A	N/A	N/A
EA		Categorical Exclusion Requested per 21 CFR 25.31(a) Adequate	08/12/2015	Sri Rama Krishnaiah, Yellela
Radiopharmaceutical		N/A	N/A	N/A
Samples Requested		N/A	N/A	N/A

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

(b) (4)

Chemistry Review Data Sheet

(b) (4)

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is Not Approvable - Minor product Quality Deficiencies. Information request 30 days letter is recommended.

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

Cyclosporine USP is a cyclic polypeptide manufactured by fermentation. It is a white to almost white powder. Its molecular weight is 1202.6 g/mol. Practically insoluble in water, Soluble in acetone, in methanol, in ethanol 96% v/v, in ether, in chloroform, and in methylene chloride. The drug substance does not exhibit polymorphism. Chemically, cyclosporine is a stable compound. Cyclosporine is official in the USP. The specifications and acceptance criteria conform to USP monograph requirements.

Cyclosporine [redacted] (b) (4)). This DMF is adequate.

II. Drug Product

The following section is not to be released under FOIA

Cyclosporine ophthalmic emulsion 0.05% contains a topical immunomodulator with anti-inflammatory effects. It is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (dry eye). Cyclosporine ophthalmic emulsion is packaged in sterile, preservative-free single-use vials (0.4 ml/each vial).

The generic product is a qualitatively (Q1) and quantitatively (Q2) equivalent ophthalmic emulsion as that of RLD. [redacted] (b) (4)

[redacted] (b) (4)

96 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Administrative

Endorsement Block

HFD-940/Sri Rama Krishnaiah, Yellela Ph.D./Primary Reviewer/08-23-2015/10-20-2016
HFD-940/Xiaoming Xu, Ph.D./Reviewer/ 12-22-2015
HFD-630/Muhammad Ashraf, Ph.D./Secondary Reviewer/08-28-2015; 12-23-2015/10-10-2016
HFD-620/Bing Cai, Ph.D./OLDP/DLBP/DD/02-16-2016/
Project Manager Name/Date: Sarah Nguyen/02-17-2016/ 10/24/2016

TYPE OF LETTER: NOT APPROVABLE due to CMC Minor Deficiencies; BE inadequate; Labeling inadequate; DMF adequate; Overall Manufacturing withhold.

Bing Cai

Digitally signed by Bing Cai
Date: 11/03/2016 02:46:32PM
GUID: 508da6ff000285eddca825bf21370b48

Muhammad Ashraf

Digitally signed by Muhammad Ashraf
Date: 11/01/2016 04:08:43PM
GUID: 508da705000289defcccfe6abe65951b

Sri Rama Krishnaiah Yellela

Digitally signed by Sri Rama Krishnaiah Yellela
Date: 10/10/2016 02:46:20PM
GUID: 508da7380002b2d9a74663c2895c10ad

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: 30- Day IR Letter***

ANDA 207606

Cyclosporine Ophthalmic Emulsion 0.05%

Apotex Inc.

Sri Rama Krishnaiah, Yellela Ph.D.

Division of Product Quality Research
Office of Testing and Research

Table of Contents

Chemistry Review Data Sheet

1. **ANDA#** : **207606**
2. **REVIEW #** : **1**
3. **REVIEW DATE** : **08/23/2015; 12/22/2015**
4. **REVIEWER** : **Sri Rama Krishnaiah, Yellela, Ph.D.**
   : **Xiaoming Xu, Ph.D.**
5. **PREVIOUS DOCUMENTS** :

Previous Document s	Document Date
None	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original Submission (Original-1)	06/18/2014
Quality/ Response to Information Request	07/07/2015
Quality/Response to Information Request	07/08/2015
Patent & Exclusivity/ Patent Certification	07/29/2015
Patent & Exclusivity/ Patent Certification	08/26/2015
Correspondence (regarding samples)	10/21/2015

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Apotex Inc.
Address:	150 Signet Drive Toronto, Ontario State Canada
Representative:	Kiran Krishnan Vice President, US Regulatory Affairs Apotex Corp 2400 North Commerce Parkway, Suite 400 Weston, FL 33326
Telephone:	954-384-3986

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name:	None
Non-Proprietary Name (USAN):	Cyclosporine Ophthalmic Emulsion 0.05%

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product:	Restasis® Ophthalmic Emulsion (Cyclosporine Ophthalmic Emulsion, 0.05%)			
Innovator Company:	Allergan Inc. NDA 050790, approval date: 12/23/2002)			
Patent Data:	As on 08/11/2015, there are 5 patents listed in the Orange Book as being relevant to this application. Generic sponsor has provided Paragraph IV Certification for all 5 patents. The sponsor has provided Paragraph II certification in respect of the patent "5474979" which expired on May 17, 2014. The RLD has two of the patient use codes U-1479 and U-1483 (Increase tear production to treat patients with Keratoconjuctivitis Sicca [Dry Eye]).			
	Patent No	**Expiry Date**	**Certification**	**Date of Submission**
	8629111	August 27, 2024	P-IV	02/27/2014
	8633162	August 27, 2024	P-IV	02/27/2014
	8642556	August 27, 2024	P-IV	02/27/2014
	8648048	August 27, 2024	P-IV	02/27/2014
	8685930	August 27, 2024	P-IV	02/27/2014
Exclusivity Data:	Firm has certified that there is no unexpired exclusivity for RLD.			

10. PHARMACOLOGICAL CATEGORY: Ophthalmic- Immune System Regulator

11. DOSAGE FORM: **Ophthalmic Emulsion**

12. STRENGTH/POTENCY: **0.05%**

13. ROUTE OF ADMINISTRATION: **Ophthalmic**

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

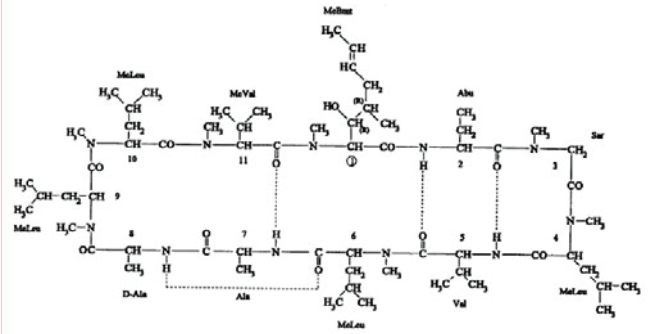
15c. PRECEDENT:

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

☒ Not a Precedent

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

Chemistry Review Data Sheet

Chemical Name	Cyclosporine
Molecular Formula	$C_{62}H_{111}N_{11}O_{12}$
Molecular Weight	1202.6 g/mol
CAS number	59865-13-3
Nomenclature:	Cyclo[[E -(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octanoyl]-L-2-aminobutyryl-Nmethylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-Nmethyl-L-valyl
Molecular Structure	

Abbreviation Key	
Sar	Sarcosine
Ala	Alanine
MeLeu	Methyl leucine
Val	Valine
MeBmt	(2S,3R,4R,6E) -2-methylamino-3-hydroxy-4-methyl-oct-6-enoic acid
MeVal	Methyl valine
Abu	Amino butyric acid

17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLE-TED
(b) (4)	II	(b) (4)	Cyclosporine USP	3	Inadequate	05/04/2015 by Jizhou Wang
	III		(b) (4)	4	NA	NA
	III			4	NA	NA

[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 050790	RLD Product

18. STATUS

CONSULTS/CMC RELATED REVIEWS		RECOMMENDATION	DATE	REVIEWER
Microbiology		**Pending Review**		
Methods Validation		N/A		
Labeling		**Pending Review**		
Bioequivalence	Dissolution	**Pending Review**		
	Bioequivalence	**Pending Review**		
Toxicology/Clinical		N/A	N/A	N/A
EA		Categorical Exclusion Requested per 21 CFR 25.31(a) Adequate	08/12/2015	Sri Rama Krishnaiah, Yellela
Radiopharmaceutical		N/A	N/A	N/A
Samples Requested		N/A	N/A	N/A

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:

(b) (4)

(b) (4)

[redacted]

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.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is Not Approvable - Minor product Quality Deficiencies. Information request 30 days letter is recommended.

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

Cyclosporine USP is a cyclic polypeptide [redacted] (b) (4) It is a white to almost white powder. Its molecular weight is 1202.6 g/mol. Practically insoluble in water, Soluble in acetone, in methanol, in ethanol 96% v/v, in ether, in chloroform, and in methylene chloride. The drug substance does not exhibit polymorphism. Chemically, cyclosporine is a stable compound. Cyclosporine is official in the USP. The specifications and acceptance criteria conform to USP monograph requirements.

[redacted] (b) (4) This DMF is currently inadequate.

II. Drug Product

The following section is not to be released under FOIA

Cyclosporine ophthalmic emulsion 0.05% contains a topical immunomodulator with anti-inflammatory effects. It is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (dry eye). Cyclosporine ophthalmic emulsion is packaged in sterile, preservative-free single-use vials (0.4 ml/each vial).

The generic product is a qualitatively Q1) and quantitatively (Q2 equivalent ophthalmic emulsion as that of RLD. [redacted] (b) (4)

(b) (4)

80 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Sincerely yours,

{See appended electronic signature page}
Bing Cai, Ph.D.
Director, Division of Liquid-based Products
Office of Lifecycle Drug Products
Center for Drug Evaluation and Research

Administrative

Endorsement Block

HFD-940/Sri Rama Krishnaiah, Yellela Ph.D. / Reviewer, 08/23/2015
HFD-940/Xiaoming Xu, Ph.D. / Reviewer, 12/22/2015
HFD-630/Muhammad Ashraf, Ph.D. /QAL, 8/28/2015; 12/23/2015
HFD-620/Bing Cai, Ph.D./DD /
Project Manager Name/Date:/Sarah Nguyen/

TYPE OF LETTER: NOT APPROVABLE due to CMC Minor Deficiency. ***30-day IR***

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207606Orig1sS000

BIOEQUILVANCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

COMPLETE RESPONSE REVIEW

ANDA No.	207606
Drug Product Name	Cyclosporine Ophthalmic Emulsion
Strength(s)	0.05%
Applicant Name	Apotex Inc.
Applicant Address	150 Signet Drive Toronto, Ontario Canada, M9L 1T9
US Contact Name	Kiran Krishnan, Senior Vice President, Global Regulatory Affairs Apotex Corp, 2400 North Commerce Parkway, Suite 400 Weston, FL 33326
US Contact Telephone Number	(954) 384-3986
US Contact Fax Number	(866) 392-1774
Original Submission Date	06/18/2014 03/12/2019 (Response to Complete Response) 07/16/2019 (Response to Information Request – Bioequivalence) 08/07/2020 (Post CR meeting Request) 06/24/2021 (Response to Complete Response Letter)
Submission Dates of Amendments Under Review	07/12/2022
Primary Reviewer	Suman Dandamudi, Ph.D.
Secondary Reviewer	Moheb Makary, Ph.D.
Tertiary Reviewer	N/A
Study Number(s)	TRC-SRT-1690
Study Type(s)	Globule Size Distribution by Dynamic Light Scattering
Strength(s)	0.05%
Analytical Site	(b) (4)
Analytical Site Address	
Study Number(s)	IVAD/20/040
Study Type(s)	In Vitro Release Study
Strength(s)	0.05%

Analytical Site	(b) (4)		
Analytical Site Address			
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** ☐ Pending ☐ 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		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1, 18, 19, and 24	**Formulation Q1/Q2**	**0.05%**	☒ Adequate ☐ Inadequate
1, 18, 19, and 24	**Globule Size Distribution**	**0.05%**	☒ Adequate ☐ Inadequate
1, 18, 19, 24 and 29	**In vitro Release Testing**	**0.05%**	☒ Adequate ☐ Inadequate

Review of a Study Amendment

1 EXECUTIVE SUMMARY

This is bioequivalence (BE) assessment of study amendment dated 07/12/2022 (supporting document # 29).

Apotex Inc., submitted its responses to the deficiency comments made by the Division of Bioequivalence III (DBIII) in the Complete Response (CR) letter dated 05/27/2022[1].

To demonstrate bioequivalence, the applicant submitted the results of globule size distribution (GSD) study using dynamic light scattering (DLS) method and in vitro drug-release testing (IVRT) on 3 lots of test and reference products. During the BE assessment of the previous amendment dated 6/24/2022, the GSD study was found to be adequate. However, the IVRT study was deemed inadequate due to the deficiencies related to the cumulative castor oil release and high variability of drug release[2].

In the current amendment, the applicant submitted acceptable responses to the deficiency comments made by DBIII. The pivotal IVRT data demonstrates that the test product has a similar drug release profile (f2>50) compared to the RLD. Thus, the IVRT study is now considered adequate.

The test product formulation is qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) product.

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**.

NOTE TO REGULATORY PROJECT MANAGER (RPM):
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 prior to contacting Policy Lead.

[1] GDRP for ANDA-207606-ORIG-1-AMEND-24, Final Decision, https://panorama.fda.gov/task/view?ID=60d636660018bd78d184f40b4c4a70f2; uploaded by Vincent Sansone on 05/27/2022
[2] GDRP for ANDA-207606-ORIG-1-AMEND-24 Bioequivalence Disciple Review, https://panorama.fda.gov/task/view?ID=60d636660018b9a535e28f3d1b36b41f; Uploaded by Yoo Jin Moon on 11/18/2021

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug product Information, PK/PD Information, and Relevant DB History

- The drug information has not changed since the original BE review completed on Oct 31, 2016. Please see the BE assessment of the original submission for details.[2]

- Per the Orange Book, currently, there is one generic product (ANDA 205894) approved for Cyclosporine Ophthalmic Emulsion, 0.05%.[3]

- There is no change in the BE recommendations for Cyclosporine Ophthalmic Emulsion[4] since the review of the previous amendment dated 6/24/2021[2].

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	--
In Vitro Release Testing	No	--
Globule Size Distribution	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendment	Yes	1

[3] Online Orange Book, Search word: Cyclosporine, https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm; Last accessed 9/6/2022

[4] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%2050790_RV09-16.pdf (Recommended Jun 2013; Revised Feb 2016; Oct 2016)

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
Deem Bioequivalent?	Yes
If not then why?	N/A

4 REVIEW OF CURRENT AMENDMENT

The deficiencies identified in the BE review was communicated to the applicant via Complete Response letter dated May 27, 2022. The applicant submitted the following responses.

Deficiency #1: You provided the castor oil release data in your method development, method validation, and pivotal in vitro release testing (IVRT) studies (Study No. IVAD/20/040). (b) (4) The cumulative data is the added-up value and should not decrease over time. Please explain the reason for the cumulative (b) (4) release pattern.

Applicant's Response: Apotex acknowledges agency's comment and would like to provide further explanation on cumulative (b) (4) release pattern. (b) (4)

(b) (4)

(b) (4)

6 RECOMMENDATIONS

The Division of Bioequivalence III (DBIII) agree that the information submitted by Apotex Inc. is adequate to demonstrate that its test product, Cyclosporine Ophthalmic Emulsion, 0.05%, submitted under ANDA 207606, 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.

7 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
None	

NOTE:
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 prior to contacting Policy Lead.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA	207606
APPLICANT	Apotex Inc.
DRUG PRODUCT	Cyclosporine Ophthalmic Emulsion, 0.05%

The Division of Bioequivalence III 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
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

8 OUTCOME PAGE

Reviewer: Suman Dandamudi **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Cyclosporine Ophthalmic Emulsion

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
49125	07/12/2022	BIO	ANDA Amendment [1]	1	1
49125	07/12/2022	Parallel	Minor Amendment (original or supplement) [1]	1	1
				Total:	2.0

DIVISION OF BIOEQUIVALENCE REVIEW

COMPLETE RESPONSE REVIEW

ANDA No.	207606
Drug Product Name	Cyclosporine Ophthalmic Emulsion
Strength(s)	0.05%
Applicant Name	Apotex Inc.
Applicant Address	150 Signet Drive Toronto, Ontario Canada, M9L 1T9
US Contact Name	Apotex Corp., Kiran Krishnan, Senior Vice President, Global Regulatory Affairs Apotex Corp, 2400 North Commerce Parkway, Suite 400 Weston, FL 33326
US Contact Telephone Number	(954) 384-3986
US Contact Fax Number	(866) 392-1774
Original Submission Date	06/18/2014
Submission Dates of Amendments Under Review	03/12/2019 (Response to Complete Response) 07/16/2019 (Response to Information Request – Bioequivalence) 08/07/2020 (Post CR meeting Request) 06/24/2021 (Current – Response to Complete Response Letter)
Primary Reviewer	Yoo Jin Moon, Pharm.D.
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.
Tertiary Reviewer	April C. Braddy, Ph.D., RAC
First Generic	Yes
Study Number(s)	TRC-SRT-1690
Study Type(s)	Globule Size Distribution by Dynamic Light Scattering
Strength(s)	0.05%
Analytical Site	(b) (4)
Analytical Site Address	
Study Number(s)	IVAD/20/040
Study Type(s)	In Vitro Release Rate Study
Strength(s)	0.05%
Analytical Site	(b) (4)

Analytical Site Address	(b) (4)		
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/DRL ☐ 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	☒ 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, 18, 19, and 24	**Formulation Q1/Q2**	**0.05%**	☒ Adequate ☐ Inadequate
1, 18, 19, and 24	**Globule Size Distribution**	**0.05%**	☒ Adequate ☐ Inadequate
1, 18, 19, and 24	**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).

Review of a Study Amendment

1 EXECUTIVE SUMMARY

This is an assessment of an amendment of response to Complete Response Letter (CRL) dated July 28, 2020.[2] Please see Section 3 Background for the history of previous amendments as well as original submission.

In response to the CRL, the applicant updated its composition table to include the exact amount of each excipient, including sodium hydroxide and water used in its test formulation. Based on the submitted information, the test product is still considered qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) product.

The applicant provided adequate additional information for its globule-size distribution (GSD) study regarding the method validation as well as the pivotal GSD study (please see Section 4.5 for details). The applicant's GSD study is now considered adequate.

In addition, the applicant re-optimized the in vitro drug-release testing (IVRT) and reconducted the study using 3 lots, each, of the test and RLD products (please see Section 5.2 for details). The pivotal IVRT data demonstrates that the test product has a similar drug release profile (f2>50) when compared to the RLD. However, the IVRT study is still considered inadequate due to the deficiencies related to the cumulative castor oil release and high variability of drug release.

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 deficiencies related to IVRT study.

The OSIS inspection status did not change since the previous assessment. The OSIS inspection status of the current ANDA is **complete**.

The application is **inadequate** with deficiencies.

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.

[2] GDRP. ANDA-207606-ORIG-1-AMEND-18. Upload Final Decision. Available at: https://panorama.fda.gov/task/view?ID=5c8a66a400b46d4a31ca0773d1f46d57; Last updated 07/28/2020.

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3 BACKGROUND

In the original submission dated June 18, 2014, Apotex Inc. submitted the results of a globule size distribution (GSD) and in vitro release testing (IVRT) study using its test product, Cyclosporine Ophthalmic Emulsion, 0.05%, to the corresponding reference product, Allergan Inc's Restasis® (cyclosporine) ophthalmic emulsion, 0.05%.[3] The formulation of the test product was considered qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) product. However, both GSD and IVRT studies were considered inadequate due to multiple deficiencies related to method validation as well as pivotal studies.

In response to the complete response letter (CRL) dated November 9, 2016[4], the applicant re-conducted its GSD and IVRT studies. However, both GSD and IVRT studies were still considered inadequate due to multiple deficiencies identified in the newly conducted method validation as well as the pivotal studies.[5]

In addition, on July 16, 2019 during the review of the CRL amendment, the applicant submitted the exact amount of Sodium Hydroxide and water used in the executive batch record in response to the Information Request Letter (IRL) dated 06/28/2019 that requested the exact amount of NaOH and water used in the formulation after an internal discussion among Office of Bioequivalence (OB), Office of Research and Standard (ORS) and Office of Generic Drug Policy (OGDP) (b) (4) .
Based on the submitted information, the test product is still considered Q1 and Q2 the same as the RLD product.

The deficiencies were communicated to the applicant via another CRL dated July 28, 2020. On August 7, 2020, the applicant requested a post-CR teleconference meeting for clarification of the GSD method validation and IVRT studies.[6]

On June 24, 2021, the applicant submitted the current amendment in response to the CRL dated 06/28/2020 and based on the post-CR teleconference meeting.

[3] GDRP. ANDA-207606-ORIG-1. Bioequivalence Primary Review. Available at: https://panorama.fda.gov/task/view?ID=542131f20042bbfed6a7f479b12981d3; Last updated 10/31/2016.
[4] GDRP. ANDA-207606-ORIG-1. Upload Final Decision. Available at: https://panorama.fda.gov/task/view?ID=576ee10e0012f941ecece7074ec5073c; Last updated 11/09/2016.
[5] GDRP. ANDA-207606-ORIG-1-AMEND-18. Available at: https://panorama.fda.gov/task/view?ID=5c8a66a300b46a51c12b4a54c6f15e51; Last updated 07/23/2020.
[6] GDRP. ANDA-207606-GI-1-MEETING-21. Meeting Minutes. Available at: https://panorama.fda.gov/task/view?ID=5f3ef03a001b4d436194b53649041305; Last updated 09/29/2020.

4 SUBMISSION SUMMARY

4.1 Drug product Information, PK/PD Information, and Relevant DB History

The PK/PD information has not been revised since the referenced review[3].

There are no approved ANDAs per Orange Book[7].

There are no changes to the BE recommendations in the draft product specific guidance as of 11/02/2021[8].

4.2 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	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	1

4.3 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
Deem Bioequivalent?	No
If not then why?	Please see deficiency letter

[7] Orange Book Online. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm; Search by "cyclosporine"; Last accessed 11/02/2021.

[8] Draft PSG for Cyclosporine ophthalmic emulsion, 0.05%; Available at: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%20050790_RV09-16.pdf; Recommended Jun 2013; Revised Feb 2016; Oct 2016

4.4 Review of Amendment Submission

Deficiency Related to Information Request (IR) Response Dated July 16, 2019

Deficiency #1: *We acknowledge that in your response dated July 16, 2019, you submitted the final composition for the exhibit batches in Module 1.2 as part of your response to the IR. However, you did not update the Components and Composition table in Module 3.2.P.1 to reflect the specific amount of each inactive ingredient added, including for those excipients which you have initially identified as having a "q.s." amount to reflect the actual amounts added to the exhibit batches used in the most recent studies (i.e., Batch #s 18EH8, 18F19, AND 18FA5). Please update the Components and Composition table with the requested information and submit to the Agency.*

Applicant's Response to the Deficiency #1: We acknowledge the agency's comment and have updated section 3.2.P.1 to provide an updated Components and Composition table (Table 2) listing the specific amount of each inactive ingredient added, including for those excipients initially identified as having a "q.s." amount. For consistency with Table 2, the IID table (Table 3) has also been updated for the Quantity per Unit (mg/mL) of Sodium Hydroxide and water for injection used.

Assessor's Comments on Applicant's Response to Deficiency #1:

- The applicant provided its formulation table in Module 3.2.P.1 as in the table below.

Strength (Label Claim):		**0.05%**				
Component Grade	**Quality Standard**	**Function**	**Quantity per Unit (g/L)**	**Quantity per Unit (mg/mL)**	**% w/w**	**% w/v**
Cyclosporine	USP	Active	0.50	0.50	(b) (4)	
Glycerin	USP	(b) (4)				
Castor Oil	USP					
Polysorbate 80 (b) (4)	NF					
Carbomer Copolymer (b) (4)	NF					
Sodium Hydroxide**	NF					
Water for Injection (WFI)	USP					
TOTAL					**100.0**	(b) (4)

(b) (4)

(b) (4)

- The applicant's response to Deficiency # 1 is acceptable.

(b) (4)

[9] 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

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BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA	207606
APPLICANT	Apotex Inc.
DRUG PRODUCT	Cyclosporine Ophthalmic Emulsion, 0.05%

The Division of Bioequivalence III (DBIII) has completed its review and has following deficiencies:

1. (b) (4)
2. In your pivotal IVRT study (Study No. IVAD/20/040), (b) (4) Please explain the reason for (b) (4) observed in the IVRT drug release data and its impact on the outcome of the study.

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

6 OUTCOME PAGE

Completed Assignment for 207606 ID: 46649

Reviewer: Moon, Yoo Jin **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Cyclosporine ophthalmic emulsion_CR amendment

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
46649	6/24/2021	BIO	ANDA Amendment [1]	1	1
46649	6/24/2021	Parallel	Request for Reconsideration [0.25]	0.25	0.25
46649	6/24/2021	Parallel	Major Amendment (original or supplement) [1.5]	1.5	1.5
46649	6/24/2021	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1
				Total:	3.75

DIVISION OF BIOEQUIVALENCE REVIEW COMPLETE RESPONSE REVIEW

ANDA No.	207606
Drug Product Name	Cyclosporine Ophthalmic Emulsion
Strength(s)	0.05%
Applicant Name	Apotex Inc.
Applicant Address	150 Signet Drive Toronto, Ontario Canada, M9L 1T9
US Contact Name and US Mailing Address	Apotex Corp., Kiran Krishnan, Senior Vice President, Global Regulatory Affairs Apotex Corp, 2400 North Commerce Parkway, Suite 400 Weston, FL 33326
US Contact Telephone Number	(954) 384-3986
US Contact Fax Number	(866) 392-1774
Original Submission Date(s)	06/18/2014
Submission Date(s) of Amendment(s) Under Review	03/12/2019 (Response to Complete Response) 07/16/2019 (Response to Information Request – Bioequivalence)
Primary Assessor	Yoo Jin Moon, Pharm.D.
Secondary Assessor	Svetlana Cherstniakova, Ph.D.
Tertiary Assessor	April C. Braddy, Ph.D., RAC
Study Number(s)	TRC-SRT-1690
Study Type(s)	Globule Size Distribution by Dynamic Light Scattering
Strength(s)	0.05%
Analytical Site	(b) (4)
Analytical Site Address	
Study Number(s)	IVAD-19-002
Study Type(s)	In Vitro Release Rate Study
Strength(s)	0.05%
Analytical Site	(b) (4)
Analytical Site Address	
Office of Study Integrity and Surveillance (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**

	☐ N/A (Waiver/Deem Bioequivalent)	☐ N/A (Waiver/Deem Bioequivalent)	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☐ Adequate ☐ Inadequate ☒ Ito be determined		
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A		
Deficiency Classification	☒ Major ☐ Minor/IR ☐ N/A (Assessment is Adequate)		
Major Deficiency Theme	New/Missing BE studies		
Justification for Major Designation	The bioequivalence deficiencies have been classified as MAJOR because the deficiencies pertain to inadequate in vitro bioequivalence studies (i.e., Globule Size Distribution and In vitro Release Test). See, e.g., 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: October 2016 RLD Number: 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, 18, and 19	**Globule Size Distribution**	**0.05%**	☐ Adequate ☒ Inadequate
1, 18, and 19	**In vitro Release Testing**	**0.05%**	☐ Adequate ☒ Inadequate

[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.

Review of a Study Amendment

1 EXECUTIVE SUMMARY

This is a review of an amendment of responses to Complete Response (CR) dated March 12, 2019 and Information Request (IR) dated July 16, 2019.

In the original submission, the formulation of the test product, Cyclosporine Ophthalmic Emulsion, 0.05% by Apotex Inc., was considered qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) product. However, both globule size distribution (GSD) and in vitro drug release testing (IVRT) were considered inadequate due to multiple deficiencies related to method validation as well as pivotal studies.[2]

In response to the CR letter, the applicant re-conducted its GSD study using dynamic light scattering (DLS) method with fresh exhibit batches of the test products and unexpired lots of RLD products. The results of the population bioequivalence (PBE) test on GSD data show that the test product meets the PBE criteria. However, the applicant's GSD study is still considered **inadequate** due to the deficiencies identified in the method validation as well as the pivotal GSD study.

The applicant also re-conducted the IVRT study using Franz diffusion cell system with nylon membrane (b) (4)). However, the applicant's membrane selection is inadequate along with its overall study design and the number of units used. Therefore, the applicant will be requested to re-evaluate its IVRT method and re-conduct the IVRT study. The IVRT study is still **inadequate**.

In addition, in response to the IR letter, the applicant submitted the exhibit batch record providing the exact amount of sodium hydroxide and water used in its test formulation (please See Section 5.1 for details). Based on the submitted information, the test product is still considered Q1 and Q2 the same as the RLD product.

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 multiple deficiencies related to GSD and IVRT studies.

Per GDRP, OSIS recommends accepting data without on-site inspections for the analytical sites.[3] In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the assessor. The OSIS inspection status of the current ANDA is **complete**.

The application is **inadequate** with deficiencies.

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[2] GDRP. ANDA-207606-ORIG-1. Bioequivalence Primary Review. Available at: https://panorama.fda.gov/task/view?ID=542131f20042bbfed6a7f479b12981d3; Last updated 10/31/2016.
[3] GDRP. ANDA-207606-ORIG-1-AMEND-18. In vitro BE Sites. Decline to inspect memo for Ritedose and Raptim. Available at: https://panorama.fda.gov/task/view?ID=5c8be28200cff4ffac426150bd9beb76&activeTab=list-task-documents; Last updated 06/28/19 and 07/31/19.

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.[2]

There is no approved ANDA per Orange Book Online. [4]

3.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
In vitro dissolution	No	-
Waiver requests	No	-
In Vitro Release Testing	Yes	1
Globule Size Distribution	Yes	1
Failed Studies	No	-
Amendments	No	1

3.3 Bioequivalence determination Request(s) For Ophthalmic Emulsions

Strength for which bioequivalence determination is requested, if applicable	0.05%
Regulation cited?	21 CFR § 320.24 (b)(6)
Strength considered for 21 CFR 320.24 (b)(6)	0.05%
Proportional to strength tested in vivo?	N/A
Is IVRT study acceptable?	No
Deem bioequivalent?	**No**
If not then why?	Due to major deficiencies in the GSD and IVRT studies.

3.4 Deficiency Comments

Please see the deficiency letter.

3.5 Recommendations

The Division of Bioequivalence III (DBIII) does not agree that the information submitted by Apotex Inc., 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

[4] Orange Book Online. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=050790; Last accessed 03/30/2020.

for ophthalmic drug products, due to the deficiencies specified in the letter. The DBIII does not deem the test product bioequivalent.

3.6 Comments for Other OGD Disciplines

Discipline	Comment
-	-

4 REVIEW OF AMENDMENT SUBMISSIONS

Pivotal Globule Size Distribution (GSD) Study

Deficiency # 1: In your GSD study, you used laser diffraction (LD) to measure GSD profile of the test and reference products. However, the LD method is not suitable for measuring the GSD of this particular drug product since laser diffraction instruments are not sensitive to accurately measure smaller-sized globules. (b) (4) (b) (4) . As a result, please measure the globule size distribution of the test and RLD products using DLS (or PCS, QELS). Please refer to the aforementioned revised guidance for FDA's recommendations in this regard. Please refer to the guidance on cyclosporine ophthalmic emulsion, referenced above, which includes information on the appropriate statistical method (EMD) to evaluate the GSD data. Please provide all details on any other statistical methods that you propose including, but not necessarily limited to, the limits that were used to declare equivalence and how those limits were determined.

Please conduct the comparative DLS study on at least three fresh exhibit lots of the test product and three unexpired lots of RLD product. As described in the aforementioned Guidance, all three test product exhibit batches should be at least 1/10th 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. The GSD data should be obtained using DLS method for three replicates for at least three units from each batch of your test and reference products.

Applicant's Response to Deficiency #1: *The comparative DLS study was conducted on three fresh exhibit lots of the test product (lots 18EH8, 18F19, and 18FA5) and three unexpired lots of RLD product (lot 97728 [expiry: 02/2020], lot 97872 [expiry: 02/2020], and lot 97781 [expiry: 01/2020],).*

As per FDA draft guidance on Cyclosporine Ophthalmic Emulsion, 0.05%, equivalence between the test product and RLD, Restasis, formulations in the shape of the globule size distribution (GSD) was demonstrated using Earth Mover's Distance method followed by a population Bioequivalence (BE) test. The population bioequivalence and Earth Mover's statistical results can be located in the Note To reviewer, located in section 5.3.1.3.

Assessor's Comments on Applicant's Response to Deficiency #1:

- In the current amendment, the applicant conducted the GSD study using Dynamic Laser Scattering (DLS) method using 3 fresh batches of the test product and 3 unexpired lots of

the reference product as recommended in the draft PSG for cyclosporine ophthalmic emulsion. The details on the evaluation of GSD study is provided in Section 5.3.

- The applicant submitted requested information. However, additional deficiencies were found during the review of GSD study as listed in comments under Section 5.3.1 and 5.3.4. Therefore, the response to deficiency # 1 is inadequate.

Deficiency # 2: Please provide Certificates of Analysis (COAs) of all RLD and test product batches to be used in the requested DLS study.

Applicant's Response to Deficiency #2: *For the Certificates of Analysis for test product batches 18EH8, 18F19, and 18FA5 please refer to section 3.2 P.5.4 and for the Certificates of Analysis of RLD batches 97728, 97872, and 97781, please refer to section 5.3.1.3.*

Assessor's Comments on Applicant's Response to Deficiency #2:

- The assessor verified the submitted COAs of all batches of the test and RLD product used in the *in vitro* BE studies.
- The applicant's response to deficiency #2 is acceptable.

Method Validation for GSD Study

Deficiency # 3: For the requested DLS study, please provide method validation data using RLD product (except for accuracy determination where standard particles should be used). Please note that the size of the standard particles should represent the size range of the cyclosporine globules.

Applicant's Response to Deficiency #3: *The validation report (TRC-SRT-1578) for the Globular Size Distribution by Dynamic Light Scattering in Cyclosporine Ophthalmic Emulsion, 0.05%, can be found in section 3.2.P.5.3. The RLD, Restasis (Lot E81145; Expiry 04/2019), was used for the validation exercises. Each standard particle sample was analyzed according to test method for Globular Size Distribution by Dynamic Laser Scattering* (b) (4)*, which can be located in section 3.2.P.5.2.*

Assessor's Comments on Applicant's Response to Deficiency #3:

- The applicant submitted the method validation study for GSD by DLS using the RLD product and standard particles (b) (4) Details on method validation study is available in Section 5.3.3.
- Although the applicant submitted requested data, additional deficiencies were found during the review of GSD method validation as listed in comments under Section 5.3.3. Therefore, the response to deficiency #3 is not acceptable.

In Vitro Release Testing (IVRT) Validation and Development

Deficiency #4: Your IVRT method development and IVRT were conducted by Absorption Systems at 436 Creamery Way, Suite 600, Exton, PA 19341. The suitability of the IVRT method

should be validated at the same site where the IVRT is conducted. Therefore, please either validate the IVRT at the testing site or provide the method transfer report between sites. Also, please include the above information in an outlined tabular format.

Applicant's Response to Deficiency #4 : *The comparative in-vitro release rate (IVRT) study of Cyclosporine from Cyclosporione Emulsion, 0.05%, Test vs. RLD formulation, has been reconducted at:*

(b) (4)

(b) (4)

Please refer to Question 8, for an outlined tabular format of the above information.

Assessor's Comments on Applicant's Response to Deficiency #4:

- In the current amendment, the method development, validation and the IVRT test took place at the same analytical site as listed above.
- The applicant's response to deficiency #4 is acceptable.

Deficiency #5: Please provide study information, protocol and validated test method for IVRT.

Applicant's Response to Deficiency #5: *Copies of the protocols and study reports for the IVRT study can be located in section 5.3.1.3. A summary of the protocols and validation reports included in this section is provided below :*

Protocols	***Reports***
	Method Development report for Cyclosporine IVRT Study from Cyclosporine Emulsion (IVRT-PSA-MD-016)
(b) (4)	*Analytical method validation report for quantitation of Cyclosporine (RRL-ANA-MVR-565)*
	Validation report for IVRT study of Cyclosporine Emulsion, 0.05% (RRL-IVRT-PSA-MVR-016)
	Comparative in-vitro release rate study of Cyclosporine from Cyclosporine Emulsion, 0.05% Test vs. RLD Formulation using Franz Diffusion Cells (IVAD/19/002-R)

Please refer to Question 8, for an outlined tabular format of the above information.

Assessor's Comments on Applicant's Response to Deficiency #5:

- The applicant submitted the requested study reports. The details on the assessment of these study reports are available in Section 5.4.
- The applicant's response to deficiency #5 is acceptable.

Deficiency #6: For IVRT method development and validation, please provide the following data/information:

a. For the IVRT method validation, you did not provide data to support the sensitivity (ability of the method to detect changes in release rate as a function of drug concentration in the formulation), selectivity (ability of the method to identify that different drug release rates from altered concentration test products are in-equivalent with respect to drug release from the reference product) and specificity (ability to accurately monitor the proportionality of changes in the release rate as a function of drug concentration in the formulation) of the IVRT method. Please provide experimental data demonstrating these attributes in your proposed method and showing the ability of your IVRT method in discriminating the effect of process variability in the production of test formulations.

b. Please explain how the dissolution medium was selected. Please provide the pH of the dissolution medium and confirm that the pH remained constant through each of your method validation studies.

c. (b) (4)

d. Please provide details on how the sample collection time points were selected for the pivotal IVRT study.

e. Please provide the recovery study data.

f. Please provide detailed technical drawings of the IVRT equipment set-up. Please provide specific experimental conditions used during IVRT.

Applicant's Response to Deficiency #6:

a. The IVRT method was validated for sensitivity, selectivity and specificity. Experiment details and data has been included in:

- *Method Development report for Cyclosporine IVRT Study from Cyclosporine Emulsion (IVRT-PSA-MD-016)*
- *Validation report for IVRT study of Cyclosporine Emulsion, 0.05% (RRL-IVRT-PSA-MVR-016)*

b. *Experiment details and data on selection of dissolution medium have been included in the Method Development report for Cyclosporine IVRT Study from Cyclosporine Emulsion (IVRT-PSA-MD-016).* (b) (4) (b) (4)

c. *Based on globule size distribution measurements using dynamic light scattering method, D90 values of undiluted samples of both Apotex Test and RLD products are around or above* (b) (4) (b) (4) (b) (4) *Detailed studies on selection of the membrane have been included in the Method Development report for Cyclosporine IVRT Study from Cyclosporine Emulsion (IVRT-PSA-MD-016)*

d. *Experiment details and data on selection of timepoints have been included in the Method Development report for Cyclosporine IVRT Study from Cyclosporine Emulsion (IVRT-PSA-MD-016)*

e. *Recovery study details and data are included in Method Development report for Cyclosporine IVRT Study from Cyclosporine Emulsion (IVRT-PSA-MD-016), Validation report for IVRT study of Cyclosporine Emulsion, 0.05% (RRL-IVRT-PSA-MVR-016)*

f. *Drawings of the IVRT equipment set-up are included in Figures 1,2,3,4 in Method Development report for Cyclosporine IVRT Study from Cyclosporine Emulsion (IVRT-PSA-MD-016). Specific experimental conditions used during IVRT are included in Comparative in-vitro release rate study report (IVAD/19/002-R).*

Assessor's Comments on Applicant's Response to Deficiency #6:

- The applicant provided the above requested data/information in its method development and validation reports. The assessment of the provided data as part of method development and validation is available in Section 5.4.3 and 5.4.4.
- (b) (4)
- Although the applicant submitted the requested data, additional deficiencies were identified during the assessment of applicant's method development and validation for IVRT in Sections 5.4.3 and 5.4.4. Therefore, the applicant's response to deficiency #6 is not acceptable.

[5] Merck Index Online. Cyclosporine. Available at: https://www.rsc.org/Merck-Index/monograph/m4020/cyclosporins%20derivative%20cyclosporin%20a?q=authorize; Last accessed 05/26/2020.

Pivotal IVRT Study

Deficiency #7: Please address the following comments for your pivotal IVRT.

a. (b) (4)

b. For IVRT study, please conduct comparative drug release testing on 12 units from exhibit batches of the test and unexpired lots of the reference products. 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.

c. Please provide the complete address of the analytical site(s) for the IVRT study.

Applicant's Response to Deficiency #7:

a (b) (4)

b. IVRT study was carried out using the validated IVRT method in compliance to the Guidance for Industry Nonsterile Semisolid Dosage Forms Scale-Up and Postapproval Changes, ln Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS) May 1997, USP < 1724>. Therefore, six units were tested from test and RLD in accordance with the recommendation in the guidance. Method validation study demonstrates that the IVRT method is able to discriminate the effect of process variability in the production of the test formulation.

c. The complete address of the analytical site(s) for the IVRT study is :

(b) (4)

Assessor's Comments on Applicant's Response to Deficiency #7:

a. The applicant was asked to provide the data as cumulative amount percentage of drug release vs. time data in SAS.xpt format. The applicant provided the drug amount in SAS.xpt format, however, did not provide in the format of cumulative amount percentage. Therefore, the applicant will be asked to resubmit the data as cumulative amount percentage of drug release vs. time.

b. The applicant was specifically asked to submit IVRT testing data on 12 units of test and reference products. However, the applicant referred to SUPAC-semisolid dosage form and submitted data of 6 units instead. As stated previously in the CR letter, (b) (4) t. In addition, the current thinking is that 12 units from 3 batches of the test product and 3 lots of the RLD product should be tested. Therefore, the applicant will be asked to reconduct IVRT using 12 units from 3 batches of the test product and 3 lots of the RLD product.

c. The applicant provided the address for the analytical site where IVRT was conducted.

- Therefore, the applicant's response to Deficiency #7 is not acceptable.

Deficiency #8: Please provide the study design, product information and method validation summary tables for the in vitro GSD BE study and IVRT. 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 No.	
Testing Method Description	
Testing Equipment Used (e.g., name, model, etc.)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc.)	
Validation Report No.	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc.)	

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		

Parameter	Acceptance Criteria	Criteria Results
Linearity		
System Precision		
Accuracy and Method Precision		
intermediate Accuracy and Method Precision		
Range		
Solution Stability		
Specificity		
Robustness		

Applicant's Response to Deficiency #8: *As requested by the Agency, the study design, product information, and method validation summary tables for the in vitro GSD BE study and IVRT, are provided below in the recommended tabular format:*

GSD BE

(b) (4)

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Assessor's Comments on Applicant's Response to Deficiency #8:

- The applicant provided the information of GSD and IVRT in the requested table format.
- The applicant's response to Deficiency #8 is acceptable.

5 APPENDIX

5.1 Formulation

In the current amendment, the applicant manufactured new exhibit batches at a new manufacturing facility. The overall components of the formulation remain the same. However, below are the changes made in the new exhibit batches.

(b) (4)

43 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Deficiencies related to the pivotal IVRT study

9. The IVRT testing should be conducted using 12 units from 3 batches of test product and 12 units from 3 lots of unexpired reference-listed drug product. The data should be presented as cumulative amount percentage (%) of drug release versus time. Based on the cumulative percentage drug release vs. time profile, please provide the calculation of model independent similarity (f2) factor for comparison.

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

6 OUTCOME PAGE

Completed Assignment for 207606 ID: 40518

Reviewer: Moon, Yoo Jin **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Cyclosporine ophthalmic emulsion

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
40518	3/12/2019	BIO	ANDA Amendment [1]	1	1
40518	3/12/2019	Parallel	Major Amendment (original or supplement) [1.5]	1.5	1.5
40518	3/12/2019	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1
40518	3/12/2019	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	1	1
				Total:	4.5

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207606
Drug Product Name	Cyclosporine Ophthalmic Emulsion
Strength(s)	0.05%
Applicant Name	Apotex Inc.
Applicant Address	150 Signet Drive Toronto, Ontario State Canada
US Contact Name and US Mailing Address	Kiran Krishnan, Vice President, US Regulatory Affairs Apotex Corp 2400 North Commerce Parkway, Suite 400 Weston, FL 33326
US Contact Telephone Number	(954) 384-3986
US Contact Fax Number	(866) 392-1774
Contact's Email	N/A
Original Submission Date(s)	June 18, 2014
Submission Date(s) of Amendment(s) Under Review	N/A
***First Generic**	No
Reviewer	Patrick E. Nwakama, Pharm.D.
Study Number(s)	MV/S/1304002
Study Type(s)	Globule Size Distribution (GSD) study by Laser Diffraction
Strength(s)	0.05%
Clinical Site	N/A
Clinical Site Address	N/A
In Vitro Test Site	Apotex Inc.
In Vitro Test Site Address	150 Signet Drive Toronto, Ontario State Canada
Study Number(s)	N/A
Study Type(s)	In vitro Drug Release Test (IVRT) study
Strength(s)	0.05%
In Vitro Test Site	(b) (4)
In Vitro Test Site Address	
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☒ **Pending** ☐ **Complete** ☐ **N/A (Waiver)** **Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☐ **Complete**
Waiver	☐ **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		
Overall Review Result	☐ Adequate ☒ Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Communication	☐ ECD ☒ IR ☐ Not Applicable		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	**Globule Size Distribution**	**0.05%**	☐ Adequate ☒ Inadequate
1	**In vitro Release Testing**	**0.05%**	☐ Adequate ☒ Inadequate
1	**Waiver**	**0.05%**	☐ Adequate ☒ Inadequate

***Reviewer's Note**: According to the ANDA Filing Checklist review (GDRP: ANDA 207606-ORIG-1/Review & Comm. Documents Filing Primary Review A207606N000DFR_CHK.doc is the first generic ANDA http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880b86272

1 EXECUTIVE SUMMARY

Apotex Inc. 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. (approved on 12/23/2002).

According to the Draft Bioequivalence (BE) Guidance for Cyclosporine Ophthalmic Emulsions (Feb 2016), to qualify for the in vitro option for this drug product, pursuant to 21 CFR 320.24 (b)(6), all of the following should be met:

i. The test and RLD formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same.

ii. The comparative physicochemical characterizations of the test and RLD formulations are acceptable. The comparative study should be performed on at least three exhibit lots of both test and RLD products[3].

iii. Acceptable comparative in vitro drug release rate tests of cyclosporine from the test and RLD formulations. The methodology used for in vitro drug release testing should

[1] Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] 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.
[3] 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.

be able to discriminate the effect of process variability in the production of the test formulation.

For the current application, the Test and the RLD products contain the same amount of active ingredient and inactive ingredients in the same concentrations. The test formulation is Q1/Q2 the same as RLD product.

To demonstrate BE, the firm provided results of globule size distribution (GSD) study using laser diffraction (LD) technique (b) (4)) method. The firm's GSD study is inadequate. Per the revised September 2016 Draft BE Guidance, applicants are recommended to use **dynamic light scattering** (DLS) method [or photon correlation spectroscopy (PCS), quasi-elastic light scattering (QELS)] to measure the globule size of the test and reference listed drug (RLD) formulations, and provide comparable size distribution profiles (intensity-weighted histograms) upon serial dilutions.

(b) (4)

On May 23, 2016, DBIII sent a consult request to Office of Regulatory Science (ORS) seeking clarification on the following questions:

1. *The firm used only the laser diffraction (LD) method to measure the globule size distribution profile of the test and RLD products in the GSD study submitted to support this ANDA. The firm did not measure GSD of the test and RLD products using a complimentary size characterization method(s) in addition to the laser diffraction method to accurately detect the entire globule size distribution. For the submitted LD results, are the modes and instrument settings of the particle size analyzer (b) (4)) appropriate for GSD measurement in the current application? In addition, we would like to know if DTP has any recommendation on whether the specified obscuration limits of (b) (4) optimal.*
2. *Are the method validation data submitted by the firm for laser diffraction (LD) method for GSD acceptable? If not, please provide specific deficiencies that can be conveyed to the firm. Additionally, the firm did not perform accuracy evaluation.*
3. *Are the GSD histograms/profiles submitted by the firm for Test product (E14001, E14004 and N00280) and RLD product (78966, 80584 and 80894) adequate? We would like DTP to review the 10-sample GSD profiles for each batch and provide recommendations on the acceptability of data and/or any deficiencies to be communicated to the firm.*

In response to the consult request from DBIII, ORS provided the current thinking [(Draft Bioequivalence (BE) Guidance for Cyclosporine Ophthalmic Emulsions (Feb 2016)] in measuring globule size distribution of cyclosporine ophthalmic emulsion (See Attachment Section for ORS Consult Response).

The firm also provided in vitro drug release test (IVRT) results using [redacted] (b) (4)) on Test (Lot # N00280 and E14001) and RLD (Lot #79237 and 80894) products. The firm analyzed IVRT data based on *Guidance for Industry: Nonsterile Semisolid Dosage Forms: SUPAC, CMC, IVRT and In Vivo BE Documentation (SS Guidance.May 1997)*[4]. According to the Office of Research and Standards (ORS)/OGD, considering Cyclosporine Ophthalmic Emulsion is not a semisolid dosage form, therefore the firm should "*also submit dissolution data in terms of cumulative percent of drug release vs. time for test and reference products"*[5]. As per OPQ Review[6], the "Overall, the IVRT method seems problematic: [redacted] (b) (4) . The firm acknowledged that the membrane does not distinguish between released and unreleased cyclosporine from the formulations and is in the process of selecting a membrane with a more suitable pore size. Therefore, IVRT study is inadequate.

In addition, the firm submitted the comparative physicochemical data on pH, osmolality, viscosity, zeta potential and surface tension for both test and RLD products in the current ANDA in accordance with the 2016 Guidance, which will be further evaluated by OPQ.

The Division of Bioequivalence III (DBIII) cannot grant the waiver request due to multiple deficiencies related to GSD and IVRT studies.

There is no inspection history for the analytical sites at Apotex (150 Signet Drive, Toronto, Ontario Canada) and [redacted] (b) (4)). The Office of Study Integrity and Surveillance (OSIS) inspection of these new analytical sites are pending for current application.

The application is **inadequate** with deficiencies.

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[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070930.pdf
[5] http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880caac1d
[6] http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880c4b88e
http://panorama.fda.gov/document/view?ID=57d1c594012670e9eb74e4bce0f963ad

2 TABLE OF CONTENTS

3 BACKGROUND

On 11/25/2015, upon DBI's request, a meeting with the Office of Pharmaceutical Quality (OPQ), the Office of Testing and Research (OTR) and the Office of Regulatory Science (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).[7]

In February 2016, the Office of Generic Drugs (OGD) posted a revised Draft Guidance on Cyclosporine Ophthalmic Emulsion[8]. 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 2015, 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 with OPQ that OGD's review responsibilities for Cyclosporine Ophthalmic Emulsion applications are:

1. Q1/Q2 sameness between the Test and Reference formulations (also reviewed by OPQ)
2. Comparative Globule Size Distribution (GSD) data
3. IVRT with respect to establishing bioequivalence

OPQ will review all comparative physicochemical characterizations except GSD.

On 5/19/2016, DBIII sent consult requests to OGD/ORS/DTP and OGD/ORS/DQMM for the current ANDA for Cyclosporine Ophthalmic Emulsion (ANDA 207606) with questions regarding the GSD and IVRT studies.[10] On 5/31/2016, DTP and DQMM provided their consult response for ANDA 207606 to DBIII.[11,12]

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[7] \\cdsnas\ogds11\DIVISION\BIO\BIO1\Meeting Minutes\DBI non-Bio Management Meeting\2016\11252015 Cyclosporine Ophthalmic Emulsion Meeting Minutes.docx.

[8] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf Recommended 06/2013, Revised 02/2016

[9] \\cdsnas\ogds11\DIVISION\BIO\BIO1\Email Reference\203880CyclosporineOphthalmicEmulsion

[10] http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880cfdf7d

[11] http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880d13d28

[12] http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880d183ec

4 SUBMISSION SUMMARY

4.1 Drug Product Information[13]

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[14]	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[5]

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 of cyclosporine ophthalmic emulsion twice a day in each eye approximately 12 hours apart
Drug Specific Issues (if any)	N/A

4.3 OGD Recommendations for Drug Product

Number of studies recommended:	2 Options: In Vitro or In Vivo Study

[13] Orange Book, Search Term: Cyclosporine, last accessed on 01/21/2016.
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=050790&TABLE1=OB_Rx
[14] Drugs@FDA: Search term: Cyclosporine, last accessed on 01/21/2016
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050790s021lbl.pdf

I. *In vitro* option:

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 criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively (Q1) and quantitatively (Q2) the same.

ii. The comparative physicochemical characterizations of the test and RLD formulations are acceptable. The comparative study should be performed on at least three exhibit lots of both test and RLD products.

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality, and surface tension. Sponsors should use complementary size characterization methods to capture the entire globule size range of the test and RLD formulations, and provide comparable size distribution profiles (histograms) for both undiluted samples and upon serial dilution. Full profiles and raw data of the globule size distributions should be submitted for all samples tested, and information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement should be provided. More than one size characterization method may be necessary to accurately detect the entire globule size distribution.

Sponsor should also 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, viscosity, pH, zeta potential, osmolality, and surface tension).

Bioequivalence based on (95% CI): Population BE based on D50 and SPAN (alternatively harmonic intensity-weighted average particle diameter and polydispersity index derived from cumulant analysis of the globule size intensity distribution) obtained from each of the complementary size measurement methods. In addition, equivalence between the test and RLD formulations in the shape of the globule size distribution (such as the presence of multiple peaks) should be demonstrated by a method proposed by the sponsor. D10, D50, D90, or the globule size at each peak detected in the RLD could be used as possible values for comparison. The other physicochemical parameters do not require population BE analysis.

iii. Acceptable comparative in vitro drug release rate tests 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.

An in vivo BE study with clinical endpoint is requested for any generic cyclosporine ophthalmic emulsion, 0.05% that has a different inactive ingredient from the RLD, a difference of more than 5% in the amount of any inactive ingredient compared to that of the RLD, or unacceptable data from in vitro comparative studies.

II. In Vivo Option

1.	**Type of study:**	BE study with clinical endpoint
	Design:	Randomized, double-blind, parallel, placebo-controlled, in vivo
	Strength:	0.05%
	Subjects:	Otherwise healthy males and females whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (KCS)
	Additional Comments:	If a sponsor opts to conduct a BE study with clinical endpoint, FDA recommends that the sponsor submit the protocol for review to the OGD Division of Clinical Review prior to conducting the study.

Bioequivalence based on:	Clinical endpoint (in vivo option)

Dissolution test method and sampling times: Not applicable

Waiver request of in-vivo testing:	Yes	
Source of most recent recommendations or provide the embedded document to the current draft guidance	FDA Draft Guidance on Cyclosporine (Recommended Jun 2013; Revised Feb 2016; Sep 2016) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf	
Summary of OGD or DB History[15,16]	Approved ANDAs:	No
	Pending ANDAs:	Yes ANDAs (b) (4) 203880 (b) (4) 207606, (b) (4) 205894)
	Protocols:	Yes[17]
	Controls	Yes[18]  CC# 10-0014 Apotex test_approval.pdf
	Pending Citizen Petitions and other legal and regulatory issues:[19] If yes, please comment.	☐ Yes ☒ No

[15] DARRTS: Search term: Cyclosporine Last accessed: 09/12/2016
[16] GDRP: Search term: Cyclosporine Last accessed: 09/14/2016
[17] OGD Division of Bioequivalence Protocols Tracking: Search term: Cyclosporine Last accessed: 09/26/2016 http://fdswv04385/seltrack/ProtocolGrid.ASP
[18] OGD - CONTROLS (Correspondence) Document Tracking: Search term: Cyclosporine Last accessed: 09/26/2016 http://cdsogd1/controls/DOCGRID.ASP
[19] Please check DLRS policy updates in the link http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx

4.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
In vitro dissolution	No	-
Waiver requests	Yes	1
In Vitro Release Testing	Yes	1
Globule Size Distribution	Yes	1
Failed Studies	No	-
Amendments	No	-

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?	See deficiencies below

4.6 Deficiency Comments

Please refer to the deficiency comments in the letter section of the review

4.7 Recommendations

The Division of Bioequivalence III (DBIII) does not agree that the information submitted by Apotex Inc. demonstrates that its test product, Cyclosporine Ophthalmic Emulsion, 0.05% base, 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 attached. The DBIII recommends the waiver of bioequivalence testing be denied.

1. The Division of Bioequivalence III (DBIII) finds the GSD study (Study Protocol # MV/S/1304002) inadequate. Apotex Inc. conducted GSD study on its test product, Cyclosporine Ophthalmic Emulsion, 0.05% (lot # N00280, E14001, and E14004) comparing it to Restasis® (cyclosporine) Ophthalmic Emulsion, 0.05% (lot # 78766, 80894 and 80584).

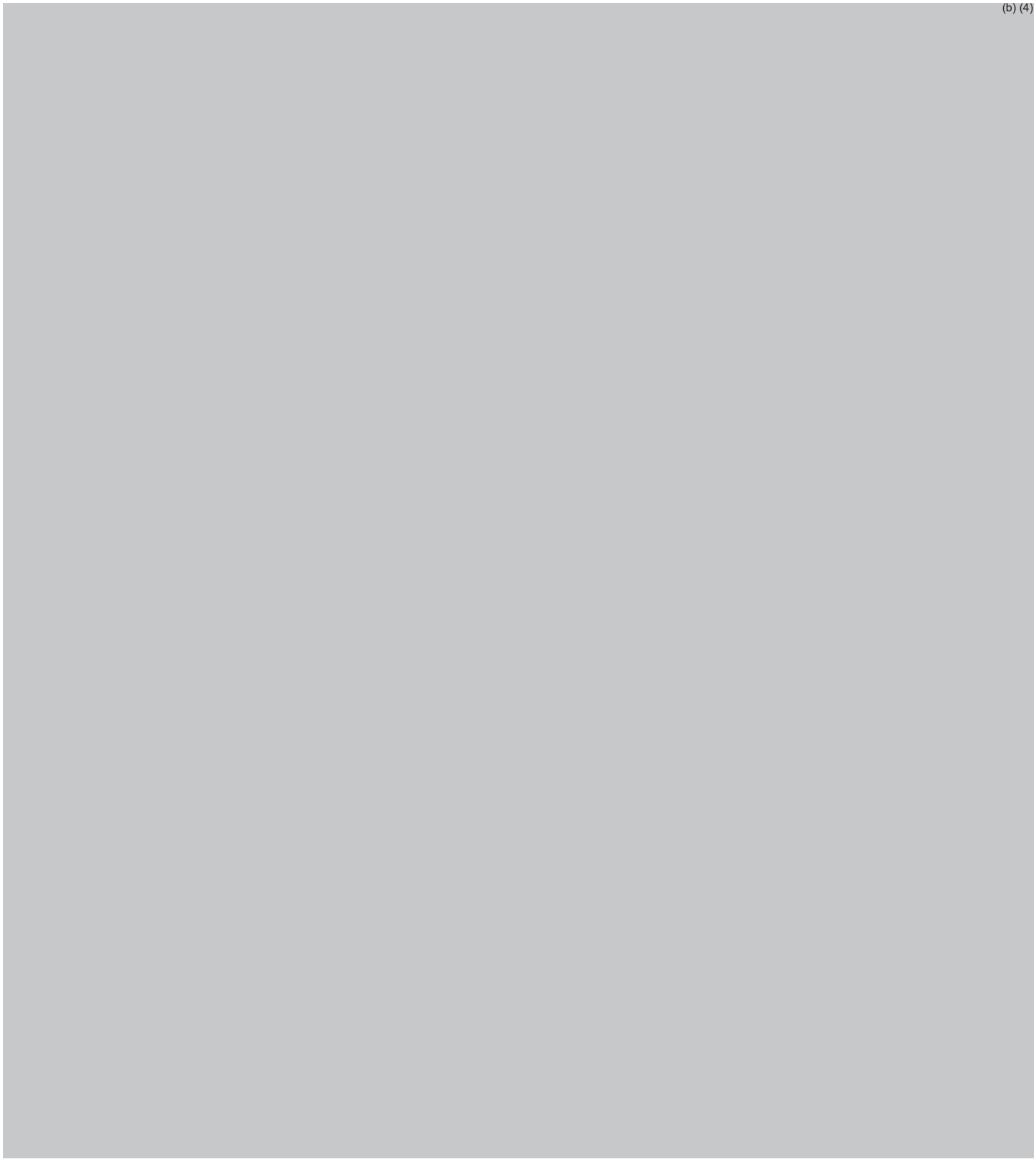
2. The Division of Bioequivalence III (DBIII) finds the IVRT study inadequate. Apotex Inc. has not conducted pivotal IVRT study on its test product, Cyclosporine Ophthalmic Emulsion, 0.05% comparing it to Restasis® (cyclosporine) Ophthalmic Emulsion, 0.05%.

4.8 Comments for Other OGD Disciplines

Discipline	Comment
Office of Pharmaceutical Quality (OPQ)	OPQ has acknowledged the firm's confirmation (b) (4) (b) (4) Carbomer Copolymer Type A (b) (4) (b) (4) and has requested the firm to update the IIG limits for the excipient (Carbomer Copolymer Type A) used in the test drug product.

5 APPENDIX

(b) (4)



Comparison of Test and RLD Formulations, 0.05% strength

Ingredient	Test Product mg/g (b) (4)	RLD Product mg/g	Difference [(T-R)/ R*100%]
Cyclosporine, USP		0.5	5%
Glycerin, USP			(b) (4)
Castor Oil, USP			
Polysorbate 80, NF			
Carbomer Copolymer type A			
Sodium Hydroxide, NF			
Purified Water, USP			

Is there an overage of the active pharmaceutical ingredient (API)?	(b) (4)
If the answer is yes, has the appropriate chemistry division been notified?	
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	No
Comments on the drug product formulation:	Acceptable.

Reviewer's Comments:

- The generic product is qualitatively (Q1) and quantitatively (Q2) same as RLD as confirmed by the Agency in CC#10-0014. Levels of the inactive ingredients are within IIG limits for emulsion dosage form via ophthalmic route. (b) (4)

- The test product's pH range was set to 6.5 to 8.0, the same as the RLD's pH stated in its labeling. (b) (4)

  Therefore, test product formulation is **adequate**.

5.2 Batch Information

The firm conducted GSD (using LD technique), viscosity, pH, zeta potential, osmolality and surface tension test with three lots each of Test and RLD as well as in vitro drug release with two lots each of Test and RLD as shown below. In addition, the firm conducted physiochemical characterization using three batches of RLD (Lot Nos.78766, 80894, and 80584) during product development.

[21] Drugs@FDA: Search term: Cyclosporine, last accessed on 04/30/2016
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050790s021lbl.pdf

Test Performed	RLD Product Lot #	Test Product Lot #
Globule size distribution	78766 (Exp. Date 09/2014) 80894 (Exp. Date 04/2015) 80584(Exp. Date 03/2015)	N00280 (Mfg Date 11/2013) E14001 (Mfg Date 01/2014) E14004 (Mfg Date 04/2014)
Viscosity		
pH		
Osmolality		
Surface Tension		
Zeta Potential		
In vitro Drug Release	79237 (Exp. Date 10/2014) 80894 (Exp. Date 04/2015)	N00280 (Mfg Date 11/2013) E14001 (Mfg Date 01/2014)
Physicochemical characterization	78766 (Exp. Date 09/2014) 80894 (Exp. Date 04/2015) 80584 (Exp. Date 03/2015)	

Reviewer's Comments

1. The firm used the same three batches of Test (Lot Nos. N00280, E14001 and E14004) and RLD (Lot Nos. 78766, 80894 and 80584) products to conduct GSD, viscosity, pH, osmolality, surface tension, and Zeta potential study; two batches of Test (Lot Nos. N00280 and E14001) and RLD (Lot Nos. 79237 and 80894) products for in vitro drug releasing test.

2. During the drug development stage, the firm used three batches of RLD (Lot Nos. 78766, 80894 and 80584) for the physicochemical characterization study.

3. The Test batch (Lot E14004) has a [redacted] (b) (4)) and did not meet the specification criteria for assay. [redacted] (b) (4) . According to the firm, Test batch #14004 was used for in vitro comparative testing but was not placed on the stability program. Per OPQ reviewer, the low assay of Test lot E14004 is not likely to have any impact on globule size distribution (see e-mail communication in the Attachment section of the current review).

Batch Analyses

Exhibit Batch Results of Cyclosporine Ophthalmic Emulsion, 0.05%

Batch analysis results for the submission batches of Cyclosporine Ophthalmic Emulsion, 0.05% are provided in the Table below.

(b) (4)

Pivotal IVRT Study

7. Please address the following comments for your pivotal IVRT.

(b) (4)

[34] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070930.pdf

36 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

c. Please provide the pH of the dissolution medium and confirm that the pH remained constant through the experiment for both the test and reference products.

d. Please provide the recovery study data for the pivotal IVRT study.

e. Please provide the complete address of the analytical site(s) for the IVRT study.

8. Please provide the study design, product information and method validation summary tables for the in vitro GSD BE study and IVRT. 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 No.	
Testing Method Description	
Testing Equipment Used (e.g., name, model, etc.)	
Operating Conditions for Testing Equipment Used (e.g., temperature, humidity, etc.)	
Validation Report No.	
Analytical Method Description	
Analytical Equipment Used (e.g., name, model, etc.)	

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		

Parameter	Acceptance Criteria	Results
Linearity		
System Precision		
Accuracy and Method Precision		
Intermediate Accuracy and Method Precision		
Range		
Solution Stability		
Specificity		
Robustness		

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

5.11 Outcome Page

ANDA: 207606

Completed Assignment for 207606 ID: 27604

Reviewer:	Nwakama, Patrick	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:			

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
27604	6/18/2014	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
27604	6/18/2014	Bioequivalence Study (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
27604	6/18/2014	Other (REGULAR)	Waiver Ophthalmic Solution	1	1
27604	6/18/2014	Quality Assessment	Quality	5	5
				Total:	8

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207606Orig1s000

OTHER REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VIII: Office of Testing and Research

Assessing Globule Size Distribution (GSD) Method

Product Background:

NDA/ANDA (review cycle):	A207606
Drug Product Name/Strength:	Cyclosporine Ophthalmic Emulsion, 0.05%
Route of Administration:	Ophthalmic
Applicant Name:	Apotex
Submissions Being Assessed:	ANDA-207606-ORIG-1, Seq. 0015, Submitted on 03/12/2019
Sections Being Assessed:	Specification: 3.2.P.5.1, seq. 0015, dated 03/12/2019 GSD method: 3.2.P.5.2, seq. 0015, dated 03/12/2019 Validation: 3.2.P.5.3, seq. 0015, dated 03/12/2019

Globule size distribution

The analytical procedure for determination of globule size in finished product is carried out using (b) (4) The method details are summarized below:

GSD Method (3.2.P.5.2, (b) (4)

	(b) (4)
Instrument	
Dispersant fluid	
Dispersant Refractive Index (RI)	
Viscosity (dispersant)	
Temperature	
Material (RI)	
Material absorption	
Measurement position	
Cell description	
Angle of measurement	
Measurement duration	
Number of Measurements	
Attenuator	
Dilution (sample preparation)	
Analysis model	
Reporting	

Validation of GSD Method (3.2.P.5.3, TRC-SRT-1578):

System suitability / accuracy /qualification	(b) (4)
Precision (repeatability, reproducibility)	
Robustness	

(b) (4)

(b) (4)

OTR assessor: Xiaoming Xu, 6/27/2020

Xiaoming Xu

Digitally signed by Xiaoming Xu
Date: 7/23/2020 12:05:54PM
GUID: 51269607000063cff9c4cbc03bb182d1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207606Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

1 September 2016

ANDA: 207-606

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
18 June 2014	18 June 2014	18 January 2016	28 April 2016
30 August 2016	30 August 2016	NA	NA

Submission History (for 2nd Reviews or higher) – NA

Applicant/Sponsor
Name: Apotex, Inc.
Address: 150 Signet Drive
Toronto, Ontario, Canada
Representative: Kiran Krishman
Vice President, US Regulatory Affairs
Aptotex Corp
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Telephone: (954) 384-3986
Fax: (866) 392-1774

Name of Reviewer: Denise A. Miller

Conclusion: Approve from a quality microbiology perspective.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original Application

2. SUBMISSION PROVIDES FOR: Manufacture of a topical ophthalmic drug product

3. (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Dosage Form: Sterile emulsion, single use product having a 0.4 mL fill in a 0.5 mL LDPE vial
- Route of Administration: Topical ophthalmic
- Strength/Potency: 0.05%

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

B. SUPPORTING/RELATED DOCUMENTS: NA

C. REMARKS: NA

Filename: A207606MR01.docx

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval from the product quality microbiology review perspective.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – NA

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

(b) (4)

B. Brief Description of Microbiology Deficiencies – There were no deficiencies noted in the information provided.

C. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
(b) (4)							

B. Final Risk Assessment - (b) (4)

(b) (4)

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block _____

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE - NA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – White emulsion in a single use dropper vial.
- Drug product composition – The drug product composition is copied from Table 13 of section 2.3.P.1 of the application into Table 1 below:

Table 1: Drug Product Composition

Components	Reference to quality standard	Function	Quantity per Unit (mg/mL)#	Overages *	Quantity per Unit (mg/mL)	% w/v
Cyclosporine	USP	Active Pharmaceutical ingredient	0.50	(b) (4)		
Carbomer 1342	(b) (4)					
Sodium hydroxide						
Castor oil						
Polysorbate 80(Tween 80)						
Glycerin						
Water for Injection						

(b) (4)

ACCEPTAB

REVIEWER COMMENT: The information is adequate.

P.2 Pharmaceutical Development

(b) (4)

3. LIST OF MICROBIOLOGY DEFICIENCIES:

ANDA: 207-606 APPLICANT: Apotex, Inc.

DRUG PRODUCT: Cyclosporine Ophthalmic Emulsion

There are no further comments from a quality microbiology perspective.

Product Quality Microbiology Review

24 June 2016

ANDA: 207-606

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
18 June 2014	18 June 2014	18 January 2016	28 April 2016

Submission History (for 2nd Reviews or higher) – NA

Applicant/Sponsor
Name: Apotex, Inc.
Address: 150 Signet Drive
Toronto, Ontario, Canada
Representative: Kiran Krishman
Vice President, US Regulatory Affairs
Aptotex Corp
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Telephone: (954) 384-3986
Fax: (866) 392-1774

Name of Reviewer: Denise A. Miller

Conclusion: Approvable

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original Application

2. SUBMISSION PROVIDES FOR: Manufacture of a topical ophthalmic drug product

3. (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Dosage Form: Sterile emulsion, single use product having a 0.4 mL fill in a 0.5 mL LDPE vial
- Route of Administration: Topical ophthalmic
- Strength/Potency: 0.05%

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

B. SUPPORTING/RELATED DOCUMENTS: NA

C. REMARKS: NA

Filename: A207606MR01.docx

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The application is approvable from a quality microbiology perspective.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – NA

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. (b) (4)

C. Contains Potential Precedent Decision(s) - ☐ Yes ☒ No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
(b) (4)							

B. Final Risk Assessment - The risk of a non-sterile product is NOT mitigated through validation studies of the aseptic process.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block _____

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE - NA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – White emulsion in a single use dropper vial.
- Drug product composition – the drug product composition is copied from Table 13 of section 2.3.P.1 of the application into Table 1 below:

Table 1: Drug Product Composition

Components	Reference to quality standard	Function	Quantity per Unit (mg/mL)#	Overages *	Quantity per Unit (mg/mL)	% w/v
Cyclosporine	USP	Active Pharmaceutical ingredient	0.50	(b) (4)		
Carbomer 1342	(b) (4)					
Sodium hydroxide						
Castor oil						
Polysorbate 80(Tween 80)						
Glycerin						
Water for Injection						

- (b) (4)

ACCEPTABLE

REVIEWER COMMENT: The information is adequate.

P.2 Pharmaceutical Development

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207606Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL AP or TA (NEW STRENGTH)**

RPM and TL: CJ & EAT

ANDA #: 207606 Applicant: Apotex Inc.
Established Product Name: Cyclosporine Ophthalmic Emulsion, 0.05%

Basis of Submission (BOS)/RLD (Application#/Proprietary Name/Applicant): N050790 / 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: 12/2/2022**

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 **9/7/2022** Labeling **8/24/2022** Clinical **n/a**	Integrated Quality Assessment: If there is no IQA, provide the applicable date(s): • Chemistry **12/13/2022** • Microbiology 9/2/2016 • Biopharmaceutics/Dissolution DMF No(s). (b) (4) Date(s) Acceptable 12/1/2022

Additional Notes (if applicable)

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 12/15/2022
Name: IM

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#: **12/15/2022**

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 = Restasis (NDA 50790) Application submission 6/18/2014 with PIV certifications to the '111, '162, '556, '048 and '930 patents (exp. 8/27/2024). Acknowledgment letter signed 7/9/2015.

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. 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). On November 13, 2018, the CAFC affirmed the Eastern District of Texas court's Final Judgment.

Allergan submitted a request 10/14/2019 the NDA '111, '162, '556, '048, '930 and '191 patents be delisted from the OB. There are no unexpired patents or exclusivities listed in the OB to the NDA. Apotex's ANDA is eligible for Full Approval.

180 Day/CGT Exclusivity Status/Landscape: Under the FDA's interpretation of "first applicant", (b) (4) . Alterntatively, if Teva (ANDA 203880) and Akorn (ANDA 204561) had been regarded as a "first applicant," both have forfeited their eligibility for 180-day exclusivity under the failure to market provision in 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: N/A
If Tentative Approval, if known, anticipated full approval date: N/A

2. *Final Decision*

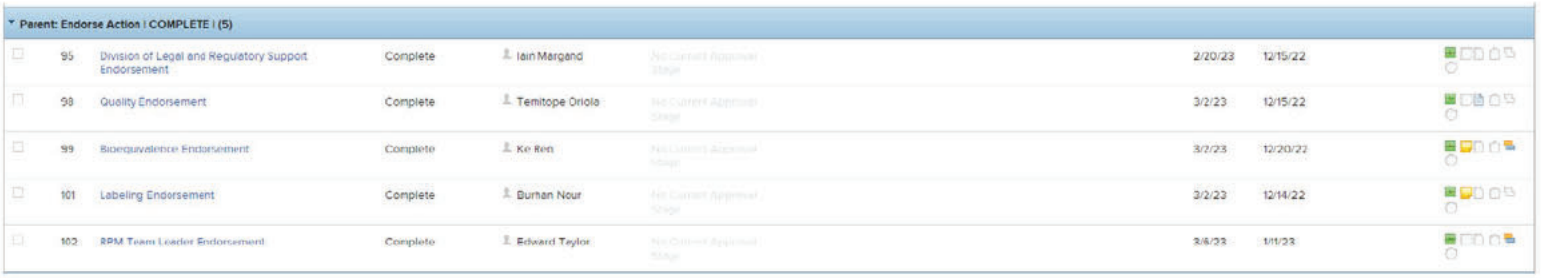
Date: **1/12/2023**
Name: **sgk**

☒ 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****



Parent: Endorse Action | COMPLETE | (5)							
95	Division of Legal and Regulatory Support Endorsement	Complete	Iain Margand		2/20/23	12/15/22	
98	Quality Endorsement	Complete	Temitope Oriola		3/2/23	12/15/22	
99	Bioequivalence Endorsement	Complete	Ke Ren		3/2/23	12/20/22	
101	Labeling Endorsement	Complete	Burhan Nour		3/2/23	12/14/22	
102	RPM Team Leader Endorsement	Complete	Edward Taylor		3/6/23	1/1/23	

Patent and Exclusivity for: N050790

Product 001
CYCLOSPORINE (RESTASIS) EMULSION 0.05%

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
Your search did not return any results							

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
Your search did not return any results		

(b) (4)

[redacted]

(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

ANDA 207606

COMPLETE RESPONSE

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

This is in reference to your abbreviated new drug application (ANDA) received for review on June 18, 2014, 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 June 24, 2021, submission, which constituted a complete response to our July 28, 2020, 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)

Labeling

6. We acknowledge that you have revised the package insert, pouch and carton labels to replace (b) (4) "Carbomer copolymer A". However, it is noted that the name of this inactive ingredient contains a typographical error as ("Carbonate Copolymer A" instead of "Carbomer Copolymer A"). Please correct the typo.

BIOEQUIVALENCE

1. You provided the castor oil release data in your method development, method validation, and pivotal *in vitro* release testing (IVRT) studies (Study No. IVAD/20/040). (b) (4)
(b) (4)

2 (b) (4)

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 aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (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 / FACILITY INSPECTIONS/EVALUATIONS / LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. 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 re-evaluated upon re-submission.

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 **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY / BIOEQUIVALENCE / LABELING

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 as 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. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore 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.

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 by 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 submission

of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Christopher Jacobs, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9946.

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

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

Vincent Sansone

Digitally signed by Vincent Sansone
Date: 5/27/2022 10:04:40AM
GUID: 508da7410002ba5d796f23a69ef57f39

ANDA 207606

INFORMATION REQUEST

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
SVP, Global Regulatory Affairs

Dear Kiran Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 24, 2021, 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. Manufacturing

(b) (4)

We request a prompt written response, no later than **July 13, 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: 7/06/2021 03:30:10PM
GUID: 56f4536500ea9700421d7152e24f140d

APOTEX
Innovating for patient affordability

APOTEX MEETING MINUTES

Meeting Type: Post-Complete Response Letter Meeting

Meeting Date and Time: September 3, 2020, 10:15 a.m.

Product: Cyclosporine Ophthalmic Emulsion, 0.05%

ANDA Applicant: Apotex Inc.

ANDA Number: 207606

ANDA APPLICANT ATTENDEES:

- Kiran Krishnan, SVP, Global Regulatory Affairs – Apotex Corp.
- Arun Prasath, VP, Global Research and Development – Apotex Corp.
- Shrikant Bhonsle, Assoc. Director, GRD Co-Development – Apotex Corp.
- Adam Steinberg, Project Manager, Regulatory Affairs – GRA-US – Apotex Corp.
- Bhupesh Singh, Associate Director, Regulatory Affairs – GRA-US – Apotex Corp.
- Ripen Misri, Director, GRD Technical & CMC Co-Dev – Apotex Inc.
- Gina Sirianni, Director, GRA Co-Development – Apotex Inc.
- Yu Chung Tsang, CSO, Biopharmaceutics-Biostatistics – Apotex Inc.
- Hareshkumar Patel, Manager, GRD Technical & CMC Co-Dev – Apotex Inc.
- Sharon Kovacs, Project Manager, GRD Technical & CMC Co-Dev – Apotex Inc.
- Javier Matienzo, Project Manager, GRA Co-Development – Apotex Inc.

FOOD AND DRUG ADMINISTRATION (FDA) ATTENDEES:
(Center for Drug Evaluation and Research (CDER))

- Christopher Jacobs, Regulatory Project Manager
- Edward Taylor, Team Leader
- Sylvia Park, Bioequivalence Project Manager
- Svetlana Cherstniakova, Lead Chemist
- Yoo Jin Moon, Staff Fellow
- Ken Ren, Acting Deputy Director, DBIII
- Colleen Lee, Regulatory Counsel

(b) (4)

Christopher Jacobs

Digitally signed by Christopher Jacobs
Date: 9/29/2020 01:47:17PM
GUID: 5a550cb600200eda21d9f0d4f7e26acb

ANDA 207606

POST-CRL MEETING
MEETING MINUTES

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on June 18, 2014, 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 post-complete response letter (post-CRL) meeting between the applicant and FDA on September 3, 2020. The purpose of the requested post-CRL meeting was to clarify deficiencies noted in the complete response letter issued by this office on July 28, 2020.

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, please contact Christopher Jacobs, Regulatory Project Manager, at (240) 402 - 9946.

Sincerely,

{See appended electronic signature page}

Christopher Jacobs
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

Meeting Type: Post-Complete Response Letter Meeting

Meeting Date and Time: September 3, 2020; 10:15 a.m. EST

Application Number: 207606

Product Name: Cyclosporine Ophthalmic Emulsion, 0.05%

Applicant Name: Apotex Inc.

Meeting Recorder: Christopher Jacobs

FDA ATTENDEES

Christopher Jacobs, Regulatory Project Manager
Edward Taylor, Team Leader
Sylvia Park, Bioequivalence Project Manager
Svetlana Cherstniakova, Lead Chemist
Yoo Jin Moon, Staff Fellow
Ke Ren, Acting Deputy Director, DBIII
Colleen Lee, Regulatory Counsel

APPLICANT ATTENDEES

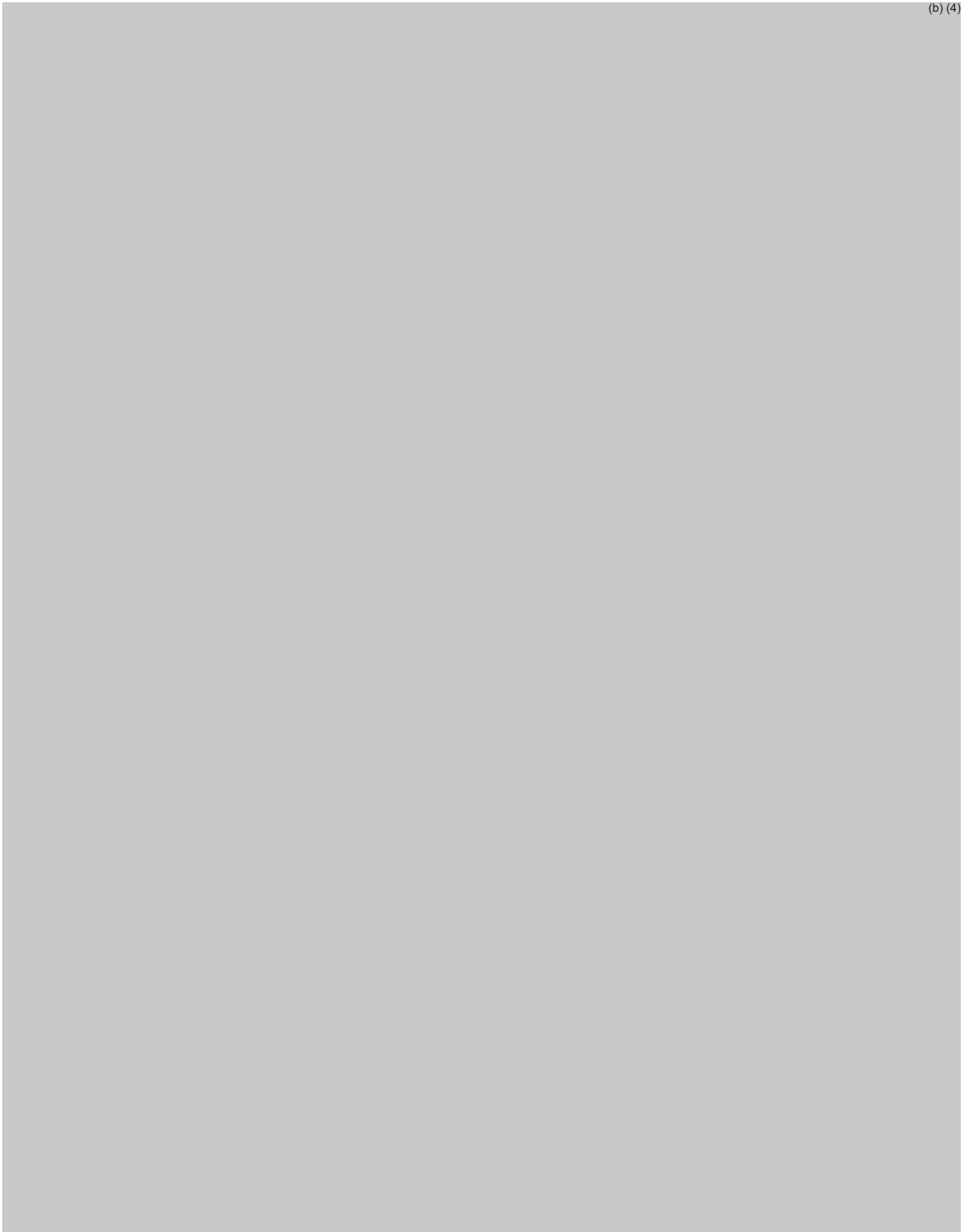
Kiran Kirshan, SVP, Global Regulatory Affairs
Arun Prasath, VP, Global Research and Development
Shrikant Bhonsle, Associate Director, GRD Co-Development
Adam Steinberg, Project Manager, Regulatory Affairs
Bhupesh Singh, Associate Director, Regulatory Affairs
Ripen Misri, Director, GRD Technical & CMC Co-Development
Gina Sirianni, Director, GRA Co-Development
Yu Chung Tsang, CSO, Biopharmaceutics-Biostatistics
Hareshkumar Patel, Manager, GRD Technical & CMC Co-Development
Sharon Kovacs, Project Manager, GRD Technical & CMC Co-Development
Javier Matienzo, Project Manager, GRA Co-Development

A. BACKGROUND

The purpose of the post-complete response letter meeting was to clarify deficiencies noted in the complete response letter dated July 28, 2020.

B. DISCUSSION

(b) (4)



3. Bioequivalence

    i. Applicant Question: We acknowledge the response from the agency. We would like to seek further clarification on whether justification based on the following could be considered as "sufficient" for a method based on incomplete release:

    IVRT principle and theory involved in the design of the method.

    Ability of the method to discriminate changes in formulation and drug product attributes.

    Demonstration of suitability of IVRT method through method validation.

    Would the agency clarify if any additional data is needed to support our justification?

    ii. FDA Response: Without further information, we cannot determine whether the mentioned information may be sufficient to support the incomplete release. However, as mentioned in the preliminary written response letter, we would like you to investigate into the release mechanism that is unique to Cyclosporine Ophthalmic emulsion using your IVRT method. Whether your justification is sufficient will be determined during the review cycle based upon the additional information submitted.

    iii. Discussion: The applicant acknowledged the responses provided by the Agency and stated that they did not have any further comments or questions at this time. The meeting ended on a note of appreciation and thanks for helping to clarify Apotex's bioequivalence concerns.

C. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

D. ACTION ITEMS

There were no action items from the meeting.

E. ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Christopher Jacobs

Digitally signed by Christopher Jacobs
Date: 9/29/2020 01:48:55PM
GUID: 5a550cb600200eda21d9f0d4f7e26acb

ANDA 207606

POST-CRL MEETING REQUEST GRANTED

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on June 18, 2014, 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 your correspondence received on August 7, 2020, requesting a post-complete response letter meeting to clarify deficiencies noted in the complete response letter issued by this office on July 28, 2020.

Your request for a post-complete response letter meeting is granted in part and the teleconference is scheduled as follows:

Date:	September 3, 2020
Time:	10:15 A.M. EST
Phone Arrangements:	+1-877-465-7975 – Access Code: 199 961 7838
CDER Participants:	Christopher Jacobs, Regulatory Project Manager Edward Taylor, Team Leader Sylvia Park, Bioequivalence Project Manager Svetlana Cherstniakova, Lead Chemist Yoo Jin Moon, Staff Fellow April Braddy, Acting Division Director, DBIII Ke Ren, Acting Deputy Director, DBIII

We have determined that your post-complete response letter meeting request contains both clarifying and non-clarifying questions. Therefore, we are denying question number one and will not provide a response to this question.

Discussion points and action items will be summarized at the conclusion of the teleconference and reflected in FDA's meeting minutes.

If you need to reschedule or cancel the post-complete response letter meeting, please notify the Agency in writing via the Electronic Submissions Gateway.

If you have any questions, please contact Christopher Jacobs, Regulatory Project Manager, at (240) 402 - 9946.

Sincerely,

{See appended electronic signature page}

Christopher Jacobs
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Christopher Jacobs

Digitally signed by Christopher Jacobs
Date: 8/20/2020 05:49:21PM
GUID: 5a550cb600200eda21d9f0d4f7e26acb

ANDA 207606

POST-CRL MEETING REQUEST
PRELIMINARY RESPONSES

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on June 18, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Cyclosporine Ophthalmic Emulsion, 0.05%.

Further reference is made to our Meeting Request Granted –Teleconference letter dated August 20, 2020.

Enclosed are our preliminary responses to the questions contained in your post-complete response letter meeting request dated August 7, 2020.

If you have any questions, call Christopher Jacobs, Regulatory Project Manager, at (240) 402 - 9946.

Sincerely,

{See appended electronic signature page}

Christopher Jacobs
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

PRELIMINARY RESPONSES

Meeting Type: Post-Complete Response Letter Meeting

Meeting Date and Time: September 3, 2020, 10:15 A.M.

The Agency provides the following preliminary responses and any additional comments in preparation for the discussion at the meeting scheduled above for your ANDA 207606. The responses do not reflect agreements, key issues, or action items. This information is shared to promote a collaborative and successful discussion at the meeting. If these answers and comments are clear to you and you determine that further discussion is not needed, you have the option of cancelling the meeting by contacting the Regulatory Project Manager via email prior to the scheduled TCON date of September 3, 2020, 10:15 A.M. In that event, these responses will constitute the official meeting response. If you determine that discussion is needed for only some of the original questions, you have the option of updating the agenda. Your updated agenda should list the questions for discussion and the order of priority. Do not submit any new data or additional questions not presented in the original meeting package, as this information will not be addressed or discussed at the meeting.

A. QUESTIONS AND FDA PRELIMINARY RESPONSES

(b) (4)

(b) (4)

Christopher Jacobs

Digitally signed by Christopher Jacobs
Date: 8/31/2020 03:12:58PM
GUID: 5a550cb600200eda21d9f0d4f7e26acb

U.S. FOOD & DRUG ADMINISTRATION

ANDA 207606

INFORMATION REQUEST

Apotex Corp.
U.S. Agent for Apotex, Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

This letter is in reference to your amendment received for review on June 18, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Cyclosporine Ophthalmic Emulsion, 0.05%.

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, including for those excipients which you have initially identified as having a "q.s." amount. 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 18EH8, 18F19, AND 18FA5) 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.

We request a complete written response no later than July 29, 2019 in order to continue our evaluation of your amendment. We will not process or review a partial response. Facsimile or e-mail responses will 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:

INFORMATION REQUEST
BIOEQUIVALENCE

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

If you do not submit a complete written response by July 29, 2019, 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, please contact Sylvia Park, Bioequivalence Project Manager, at Sylvia Park@fda.hhs.gov or 301-796-5469.

Sincerely,

{See appended electronic signature page}

Sylvia Park, Pharm.D.
OFFICE OF BIOEQUIVALENCE
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Sylvia Park

Digitally signed by Sylvia Park
Date: 6/28/2019 12:37:46PM
GUID: 5c8a87ae00acf2424a38962db1c1ad1d

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: 7/31/2019

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: ANDA 207606

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) 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 April 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: ANDAs (b) (4)

The final classification for the inspection was No Action Indicated (NAI) for the following observation:

- Failure to store the bioequivalence (BE) reserve samples with access limited to authorized personnel. Specifically, all employees of the site who had card reader access to the warehouse had access to the storage room holding the BE reserve samples of test article and reference standard from Study (b) (4)

OSIS determined that this finding did not impact the reliability of study data. In addition, in the site's written response to the observations, the site outlined the corrective actions implemented. Specifically, the site indicated that the doors to the reserve sample area are locked and a card reader has been installed to control access to the area. In addition, proximity card access has been designated to authorized personnel only.

As a result, OSIS determined that an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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: 6/28/2019

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: ANDA 207606
(b) (4)

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) 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 March 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs (b) (4).

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observations pertaining to in vivo BE study conduct only:

- (b) (4)

After receiving a written response from the site, OSIS determined that the observed objectionable conditions impacted the reliability of the 5 studies noted above and should not be used to support a regulatory decision. However, it was determined that data from in vitro studies BE/18/024 and IVAD/18/001, supporting ANDAs 207127 and 211354, respectively, were reliable to support a regulatory decision (OSIS EIR review – March 2019 Inspection).

Therefore, based on the rationale described above, an inspection is not warranted at this time for the in vitro studies conducted in support of the current ANDAs (ANDAs 207606 and 210999).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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: January 2, 2018

FROM: Anh Pham
Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

TO: Abbreviated New Drug Application (ANDA) 207606, Apotex Inc., for Cyclosporine Ophthalmic Emulsion, 0.05%

This memorandum documents certain facts that form the basis for the denial of Allergan, Inc.'s citizen petition dated August 4, 2017 and supplement dated October 13, 2017 (FDA-2017-P-4745). As of January 2, 2018, ANDA 207606 for Cyclosporine Ophthalmic Emulsion, 0.05% remains pending.

This application was submitted by Apotex Inc. on June 18, 2014 and received for review on June 18, 2014. On November 9, 2016, FDA issued a complete response (CR) letter to Apotex Inc. As of January 2, 2018, Apotex Inc. has not yet resubmitted ANDA 207606 to respond to the deficiencies identified in FDA's November 9, 2016 CR letter. Based on current information, the review of the application will not be completed when the petition response is due under 505(q) of the Federal Food, Drug, and Cosmetic Act.[1]

Three Center for Drug Evaluation and Research offices have been consulted about the petition and supplement: (1) the Office of Generic Drugs; (2) the Office of Pharmaceutical Quality; and (3) the Division of Transplant Ophthalmology Products within the Office of Antimicrobial Products. Because the petition raises issues that are connected to approvability of the ANDA, the draft consult responses remain pending with the Office of Regulatory Policy as of January 2, 2018.

Anh Pham

Digitally signed by Anh Pham
DN: cn=Anh Pham, o=FDA, ou=CDER/OGD/ORO/DPM, email=anh.pham@fda.hhs.gov, c=US
Date: 2018.01.02 17:15:33 -05'00'

[1] The completion of a review cycle and the issuance of a Complete Response or discipline review letter does not indicate that review of the application has been completed for purposes of determining whether it is appropriate to respond substantively to a petition governed by section 505(q) raising an issue that is directly applicable to the pending ANDA.

Anh Pham

Digitally signed by Anh Pham
Date: 1/02/2018 05:48:54PM
GUID: 54e4c56f00060bb2c61b878bc7a7bf95

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207606

COMPLETE RESPONSE RESUBMISSION
EXTENSION REQUEST - GRANTED

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This notification is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cyclosporine Ophthalmic Emulsion, 0.05%.

We refer you to our complete response (CR) letter dated November 9, 2016, which detailed the deficiencies identified during our review of your ANDA. After receiving a CR letter, an applicant must take one of the following actions: resubmit the ANDA addressing all the deficiencies in the letter; withdraw the ANDA; or request an opportunity for hearing, pursuant to 21 CFR 314.110(b)(1), 21 CFR 314.110(b)(2), and 21 CFR 314.110(b)(3), respectively. Additionally, the Agency may consider an applicant's failure to take an action described in 21 CFR 314.110(b) within one year after issuance of a CR letter to be a request by the applicant to withdraw the ANDA (21 CFR 314.110(c)(1)).

You submitted a letter dated September 21, 2017, requesting an extension of time to respond to our CR letter. In your correspondence you requested that FDA grant an extension until November 10, 2018 to respond to our CR letter. Upon review of your letter and the basis for an extension contained therein, we are granting your request.

Please resubmit the ANDA addressing all deficiencies identified in our CR letter, in conformance with the extension date set forth in your letter dated September 21, 2017. Please note that FDA may consider an applicant's failure to resubmit the application within the extended time period or to request an additional extension to be a request by the applicant to withdraw the application (21 CFR 314.110(c)(1)).

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 further questions, contact Anh Pham, Regulatory Project Manager Team Lead, at (240) 402-4686.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Anh Pham

Digitally signed by Anh Pham
Date: 10/11/2017 05:18:18PM
GUID: 54e4c56f00060bb2c61b878bc7a7bf95