CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 216935

Name: Prednisone Acetate; 1%

Sponsor: Lupin Limited

Approval Date: August 02, 2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216935

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216935

APPROVAL LETTER

ANDA 216935

ANDA APPROVAL

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior Vice President, Regulatory Affairs

Dear Kalpana Vanam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

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 April 4, 2024, 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 Prednisolone Acetate Ophthalmic Suspension USP, 1%, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Pred Forte Ophthalmic Suspension, 1%, of AbbVie Inc.

Reference is also made to FDA's Competitive Generic Therapy Designation – Grant letter dated March 15, 2022.

We note that Lupin Limited (Lupin) was granted a Competitive Generic Therapy (CGT) designation for Prednisolone Acetate Ophthalmic Suspension USP, 1%. Lupin is the "first approved applicant" for Prednisolone Acetate Ophthalmic Suspension USP, 1%, as defined in section 505(j)(5)(B)(v)(III) of the FD&C Act. Therefore, with this approval, Lupin is eligible for 180 days of CGT exclusivity for Prednisolone Acetate Ophthalmic Suspension USP, 1%, under section 505(j)(5)(B)(v) of the FD&C Act. This exclusivity begins to run from the date of the first commercial marketing of the CGT (including the commercial marketing of the listed drug) by Lupin, as specified in section 505(j)(5)(B)(v) of the FD&C Act. Furthermore, in accordance with section 505(j)(5)(B)(v)(I) of the FD&C

For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216935

LABELING

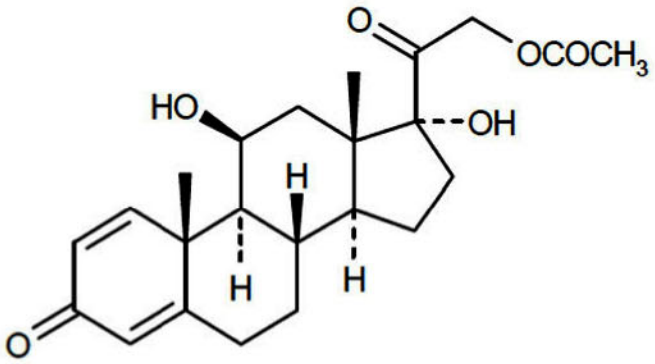
Prednisolone Acetate Ophthalmic Suspension USP,1%

STERILE

Rx Only

DESCRIPTION

Prednisolone acetate ophthalmic suspension USP, 1% is a sterile, topical anti-inflammatory agent for ophthalmic use. Its chemical name is 11ß,17, 21-Trihydroxypregna-1,4-diene-3, 20-dione 21-acetate and it has the following structure:



Prednisolone Acetate

Each mL of prednisolone acetate ophthalmic suspension USP contains:

Active: prednisolone acetate (micronized) 1%

Inactive: benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection.
The pH during its shelf life ranges from 5.0 to 6.0.

CLINICAL PHARMACOLOGY

Prednisolone acetate is a glucocorticoid that, on the basis of weight, has 3 to 5 times the anti-inflammatory potency of hydrocortisone. Glucocorticoids inhibit the edema, fibrin deposition, capillary dilation, and phagocytic migration of the acute inflammatory response, as well as capillary proliferation, deposition of collagen, and scar formation.

INDICATIONS AND USAGE

Prednisolone acetate ophthalmic suspension is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

CONTRAINDICATIONS

Prednisolone acetate ophthalmic suspension is contraindicated in acute untreated purulent ocular infections, in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Prednisolone acetate ophthalmic suspension is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS

Prolonged use of corticosteroids may result in posterior subcapsular cataract formation and may increase intraocular pressure in susceptible individuals, resulting in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Prolonged use may also suppress the host immune response and thus increase the hazard of secondary ocular infections.

If this product is used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be checked frequently.

Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation.

Acute purulent infections of the eye may be masked or activity enhanced by the presence of corticosteroid medication.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution; frequent slit lamp microscopy is recommended.

Prednisolone acetate ophthalmic suspension contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

General

The initial prescription and renewal of the medication order beyond 20 milliliters of prednisolone acetate ophthalmic suspension should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid applications, fungal invasion should be suspected in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate.

Information for Patients
Advise patients that if eye inflammation or pain persists longer than 48 hours or becomes aggravated, they should consult a physician.

Advise patients that to prevent eye injury or contamination, care should be taken to avoid touching the bottle tip to eyelids or to any other surface. The use of this bottle by more than one person may spread infection. Keep bottle tightly closed when not in use. Keep out of the reach of children.

Advise patients that prednisolone acetate ophthalmic suspension contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to application of prednisolone acetate ophthalmic suspension and may be reinserted 15 minutes following its administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been conducted in animals or in humans to evaluate the potential of these effects.

Pregnancy
Prednisolone has been shown to be teratogenic in mice when given in doses 1 to 10 times the human dose. Dexamethasone, hydrocortisone, and prednisolone were ocularly applied to both eyes of pregnant mice five times per day on days 10 through 13 of gestation. A significant increase in the incidence of cleft palate was observed in the fetuses of the treated mice. There are no adequate well-controlled studies in pregnant women. Prednisolone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from prednisolone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness in pediatric patients have been established. Use in pediatric patients is supported by evidence from adequate and well-controlled studies of prednisolone acetate ophthalmic suspension in adults with additional data in pediatric patients.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
The following adverse reactions have been identified during use of Prednisolone acetate ophthalmic suspension. Because 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.

Adverse reactions include elevation of intraocular pressure (IOP) with possible development of glaucoma and infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing.

The development of secondary ocular infection (bacterial, fungal, and viral) has occurred. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used (*see PRECAUTIONS*).

Other adverse reactions reported with the use of prednisolone acetate ophthalmic suspension include: allergic reactions; dysgeusia; eye pain; foreign body sensation; headache; pruritus; rash; transient burning and stinging upon instillation and other minor symptoms of ocular irritation; urticaria; and visual disturbance (blurry vision).

Keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodation and ptosis have occasionally been reported following local use of corticosteroids. Corticosteroid-containing preparations have also been reported to cause acute anterior uveitis and perforation of the globe.

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Overdosage will not ordinarily cause acute problems. If accidentally ingested, drink fluids to dilute.

DOSAGE AND ADMINISTRATION

Shake well before using. Instill one to two drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased if necessary. Care should be taken not to discontinue therapy prematurely.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated (*see PRECAUTIONS*).

HOW SUPPLIED

Prednisolone acetate ophthalmic suspension USP, 1% is supplied sterile in opaque white bottle with opaque white nozzle with pink cap as follows:

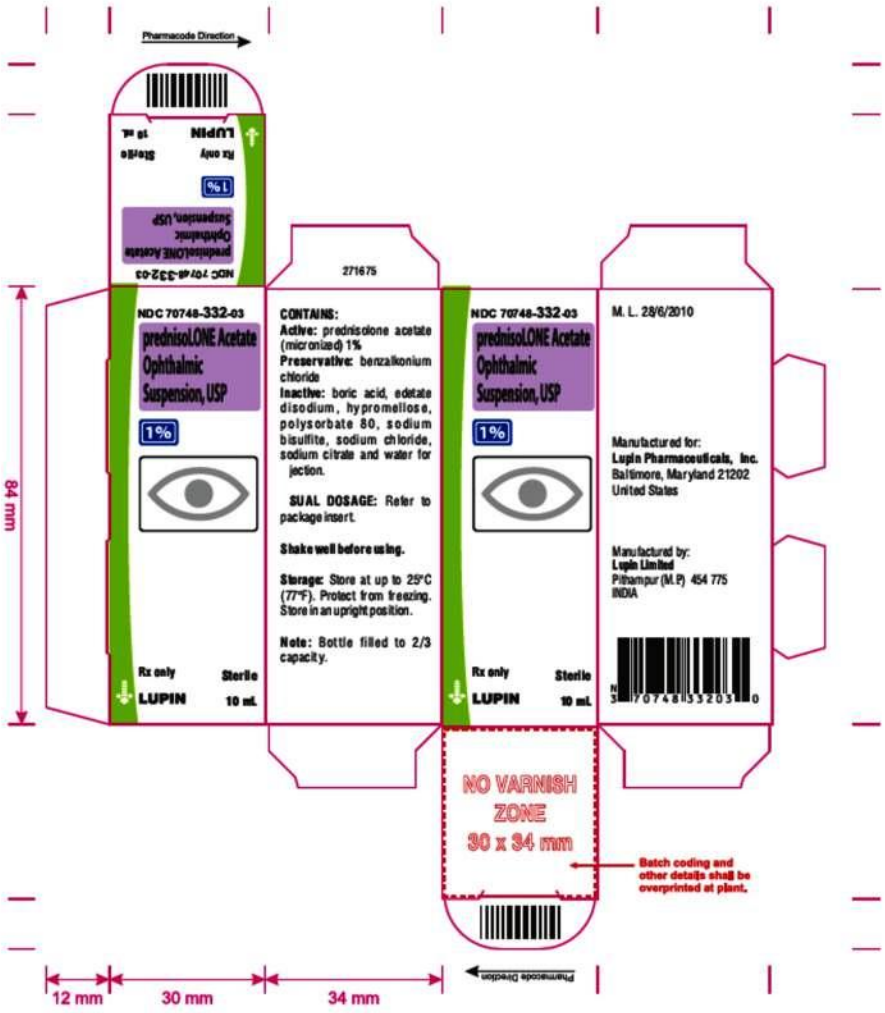
NDC 70748-332-02: 5 mL in 10 mL bottle
NDC 70748-332-03: 10 mL in 15 mL bottle
NDC 70748-332-04: 15 mL in 15 mL bottle

Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.

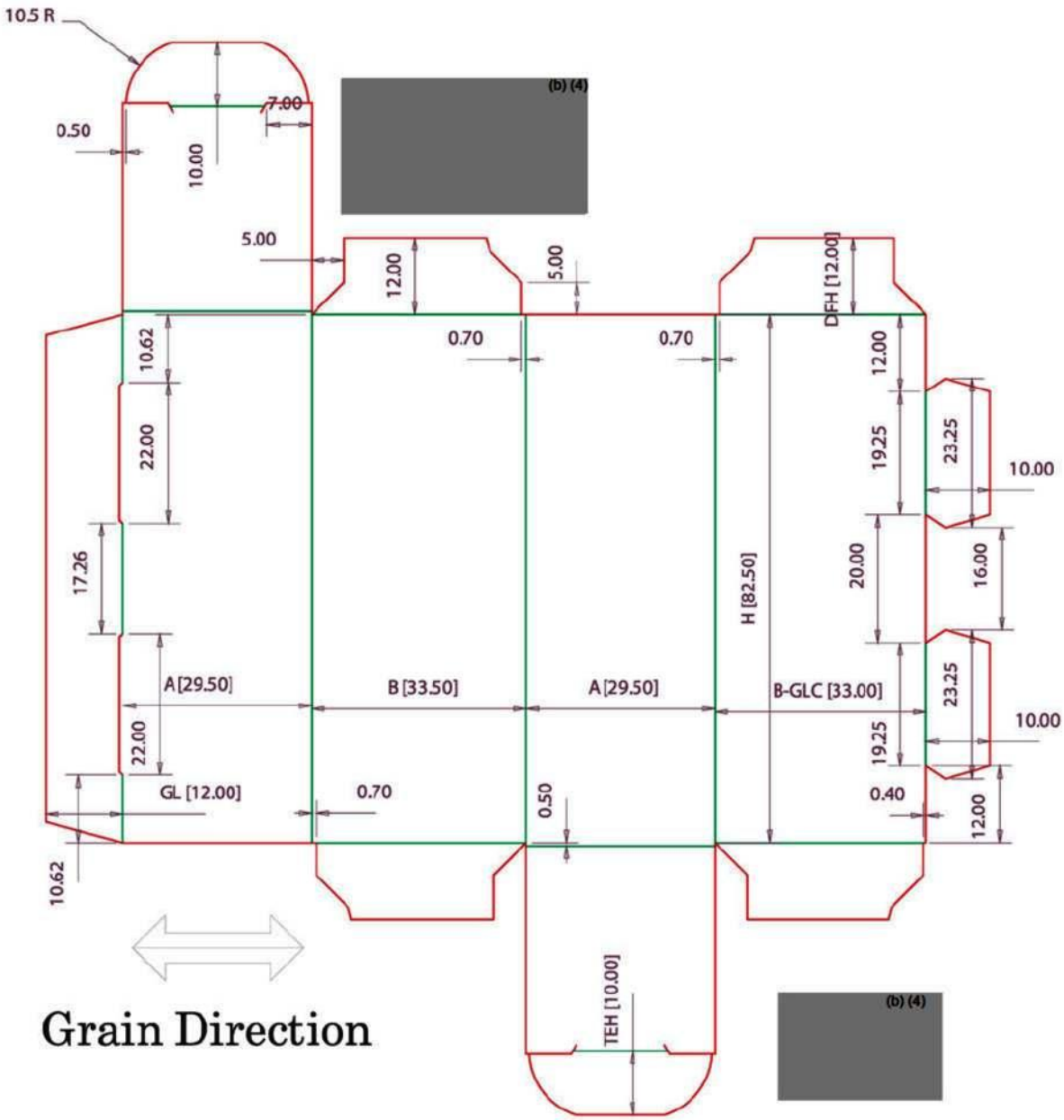
Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States.

Manufactured by:
Lupin Limited
Pithampur (M. P.) - 454 775
India.

Revised: September 2022


Pharmacode Direction
NDC 70748-332-03
prednisoLONE Acetate Ophthalmic Suspension, USP
1%
Rx only
Sterile
10 mL
LUPIN
271675
CONTAINS:
Active: prednisolone acetate (micronized) 1%
Preservative: benzalkonium chloride
Inactive: boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection.
USUAL DOSAGE: Refer to package insert.
Shake well before using.
Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 2/3 capacity.
M. L. 28/6/2010
Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States
Manufactured by:
Lupin Limited
Pithampur (M.P) 454 775
INDIA
NO VARNISH ZONE
30 x 34 mm
Batch coding and other details shall be overprinted at plant.
84 mm
12 mm
30 mm
34 mm

(b) (4)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(b) (4)
7.00
0.50
10.00
5.00
12.00
5.00
DFH [12.00]
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0.70
10.62
22.00
12.00
19.25
23.25
10.00
17.26
H [82.50]
20.00
16.00
A [29.50]
B [33.50]
A [29.50]
B-GLC [33.00]
23.25
10.00
22.00
19.25
GL [12.00]
0.70
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0.40
12.00
10.62
Grain Direction
TEH [10.00]
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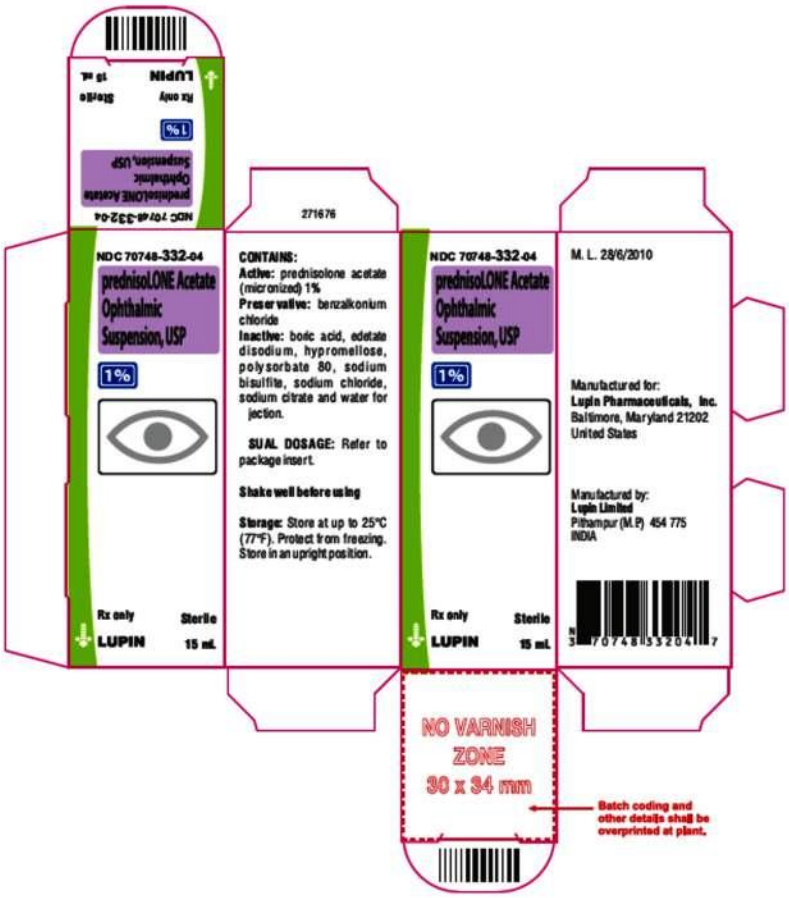
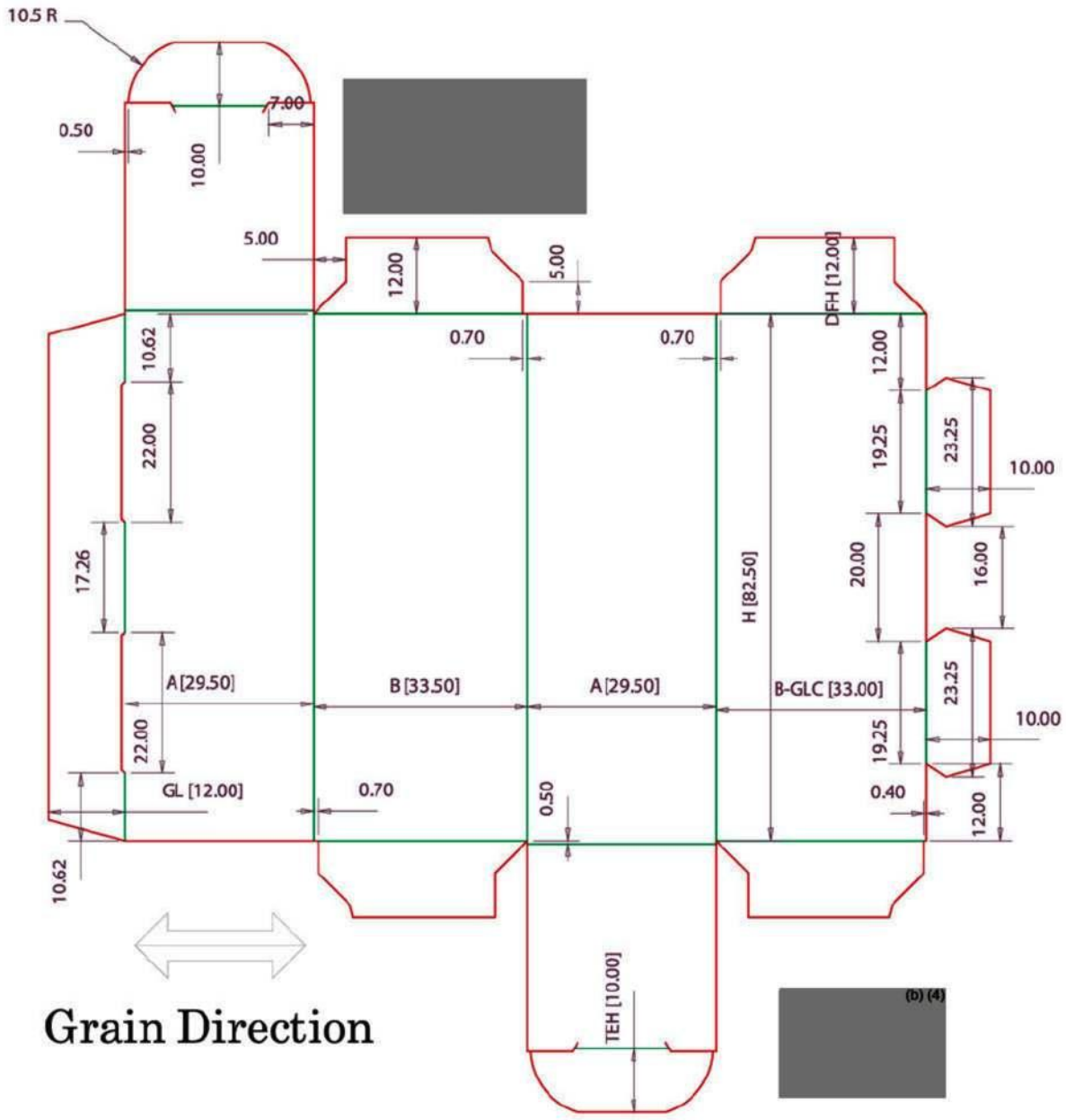

NDC 70748-332-04
prednisoLONE Acetate Ophthalmic Suspension, USP
1%
Rx only
Sterile
15 mL
LUPIN
271676
CONTAINS:
Active: prednisolone acetate (micronized) 1%
Preservative: benzalkonium chloride
Inactive: boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection.
USUAL DOSAGE: Refer to package insert.
Shake well before using
Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.
M. L. 28/6/2010
Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States
Manufactured by:
Lupin Limited
Pithampur (M.P) 454 775
INDIA
NO VARNISH ZONE
30 x 34 mm
Batch coding and other details shall be overprinted at plant.

(b) (4)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7.00
0.50
10.00
5.00
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DFH [12.00]
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0.70
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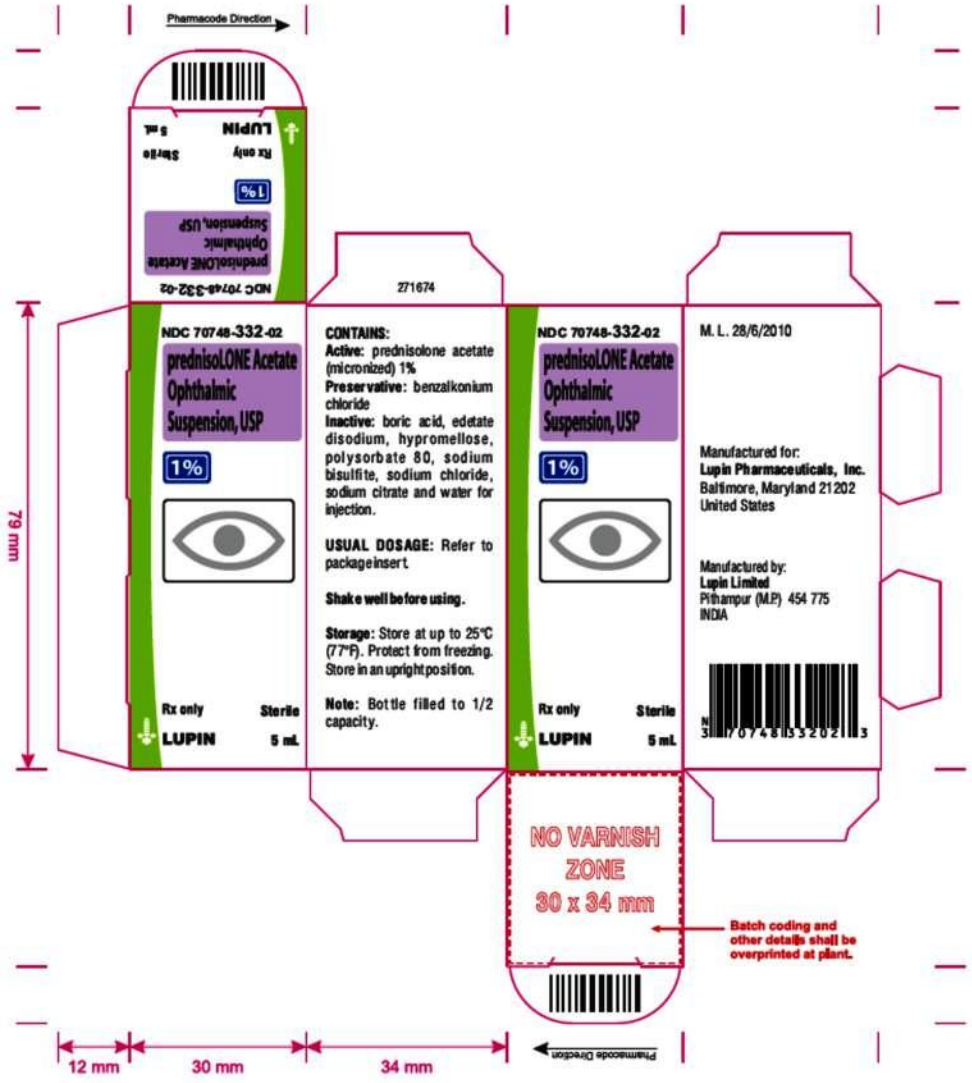
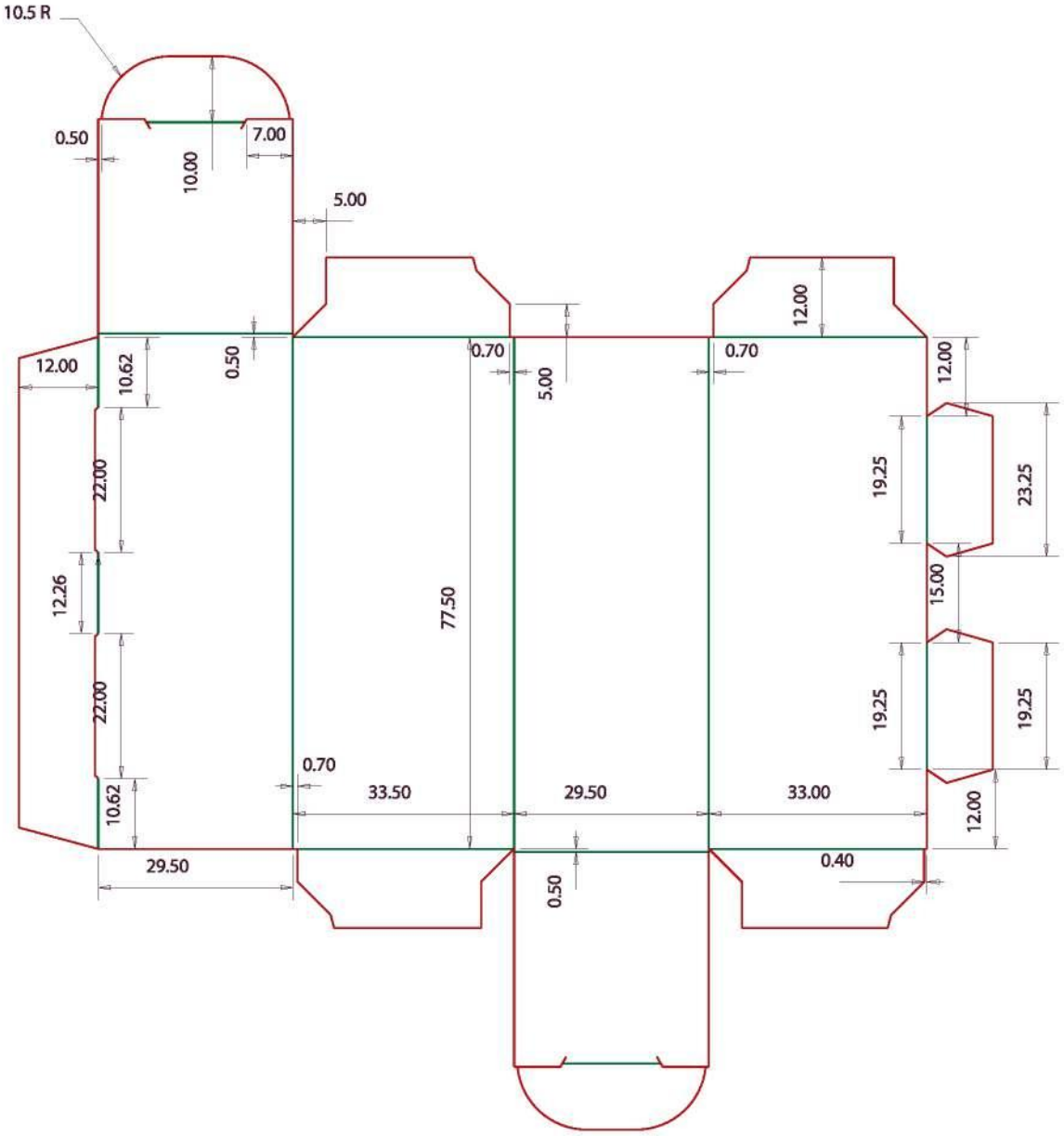
22.00
17.26
A [29.50]
B [33.50]
A [29.50]
H [82.50]
B-GLC [33.00]
12.00
19.25
23.25
10.00
20.00
16.00
22.00
GL [12.00]
0.70
0.50
0.40
12.00
10.62
TEH [10.00]
(b) (4)
Grain Direction


Pharmacode Direction
NDC 70748-332-02
prednisoLONE Acetate Ophthalmic Suspension, USP
1%
Rx only
Sterile
5 mL
LUPIN
271674
CONTAINS:
Active: prednisolone acetate (micronized) 1%
Preservative: benzalkonium chloride
Inactive: boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection.
USUAL DOSAGE: Refer to package insert.
Shake well before using.
Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 1/2 capacity.
M. L. 28/6/2010
Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States
Manufactured by:
Lupin Limited
Pithampur (M.P) 454 775
INDIA
NO VARNISH ZONE
30 x 34 mm
Batch coding and other details shall be overprinted at plant.
79 mm
12 mm
30 mm
34 mm

(b) (4)


10.5 R
0.50
7.00
10.00
5.00
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0.70
12.00
12.00
10.62
0.50
5.00
19.25
23.25
22.00
12.26
77.50
15.00
22.00
19.25
19.25
0.70
10.62
33.50
29.50
33.00
12.00
29.50
0.40
0.50

NDC 70748-332-03

prednisoLONE Acetate Ophthalmic Suspension, USP

1%

Rx only

LUPIN

STERILE

10 mL

CONTAINS: Active: prednisolone acetate (micronized) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Refer to package insert.
Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.
Shake well before using.
Note: Bottle filled to 2/3 capacity.
Manufactured by: **Lupin Limited**
Pithampur (M.P.) 454 775, INDIA
M. L. 28/6/2010 XXXXX

N 3 07481 33203 1 0

OPZ Area

Pharmacode

LOT NO.

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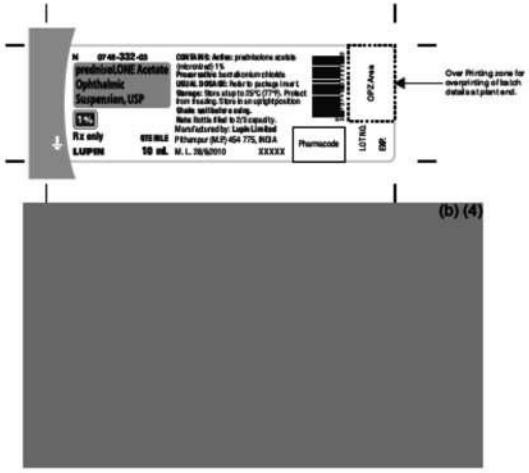
Enlarged 300%

Unwinding Direction



NDC 70748-332-04

prednisoLONE Acetate Ophthalmic Suspension, USP

1%

Rx only **STERILE**

LUPIN **15 mL**

CONTAINS:
Active: prednisolone acetate (micronized) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Refer to package insert.
Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.
Shake well before using.

Manufactured by:
Lupin Limited
Pithampur (M.P.) 454 775, INDIA
M. L. 28/6/2010 XXXXX

Pharmacode

OPZ Area

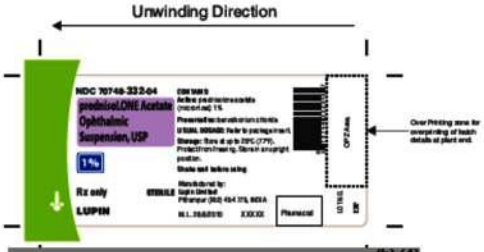
LOT NO.

EXP.

Over Printing zone for overprinting of batch details at plant end.

Enlarged 300%

Unwinding Direction



(b) (4)

NDC 70748-332-02

prednisoLONE Acetate Ophthalmic Suspension, USP

1%

Rx only

LUPIN

STERILE

5 mL

CONTAINS: Active: prednisolone acetate (micronized) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Refer to package insert.
Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.
Shake well before using.
Note: Bottle filled to 1/2 capacity.

Manufactured by: **Lupin Limited**
Pithampur (M.P.) 454 775, INDIA
M. L. 28/6/2010

XXXXX

Pharmacode

OPZ Area

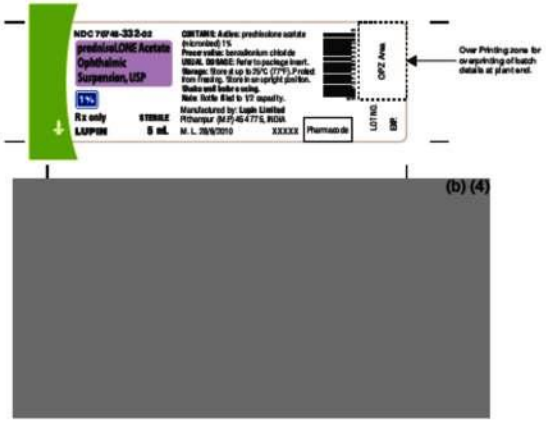
LOT NO.

EXP.

Over Printing zone for overprinting of batch details at plant end.

Enlarged 300%

Unwinding Direction



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216935

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	December 8, 2023
ANDA Number(s)	216935
Review Number	3
Applicant Name	Lupin Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Prednisolone Acetate Ophthalmic Suspension USP, 1%
Proposed Proprietary Name	N/A
Submission Received Date	October 17, 2023
Primary Labeling Reviewer	Andrew Tran
Secondary Labeling Reviewer	Marshall Florence

Review Conclusion

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

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

TABLE OF CONTENTS

1 LABELING COMMENTS (C3)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C3)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C3)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received October 17, 2023.

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

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

1.3 POST-APPROVAL REVISIONS (C3)

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

2 INSTRUCTIONS FOR ASSESSMENT (C3)

General Comments:

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

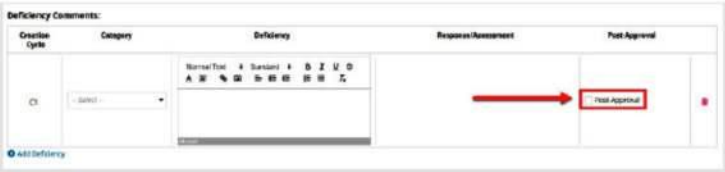
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

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

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

Deficiency Comments:

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



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C3)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	5 mL, 10 mL and 15 mL bottles	09/02/2022	Satisfactory
Blister	N/A	N/A		
Carton	Final	1 bottle per carton	10/17/2023	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	09/2022	09/02/2022	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C3)

4.1 REGULATORY INFORMATION (C3)

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

4.2 MODEL PRESCRIBING INFORMATION (C3)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**
(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)
NDA#/Supplement# (S-000 if original): NDA017011 / S-050
Supplement Approval Date: 06/06/2018
Proprietary Name: Pred Forte
Established Name: Prednisolone Acetate
Description of Supplement:

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
This Prior Approval supplemental new drug application provides for the addition of "eye pain" to the ADVERSE REACTIONS section of the Package Insert. **Link:** https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4274208_3853476_090140af8049e7fe_NDA017011_2689668
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

Reviewer Assessment:

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

Reviewer Comments:
CMC S-051, approved 06/19/2020 - CBE changing cap color from white to pink
CMC S-052 and S-053 did not affect labeling.

There are no pending supplements.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C3)

The Orange Book was searched on 12/08/2023

Table 4 provides Orange Book patents for the Model Labeling (NDA017011) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
	N/A						

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

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

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

Reviewer Comments: There are no patents or exclusivities listed in the Orange Book. **Deficiency Comments:**

4.4 UNITED STATES PHARMACOPEIA (USP) (C3)

The USP was searched on 12/08/2023

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	Yes		Prednisolone Acetate Ophthalmic Suspension	Packaging and storage—Preserve in tight containers
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

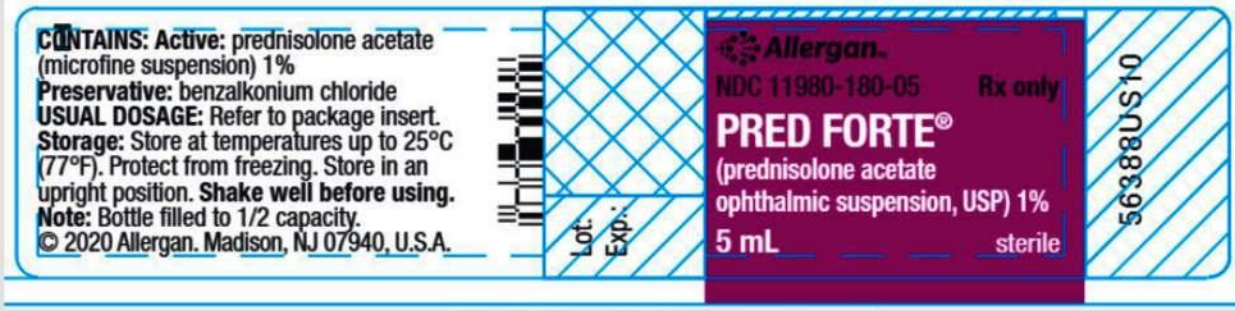
Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.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

Reviewer Comments:

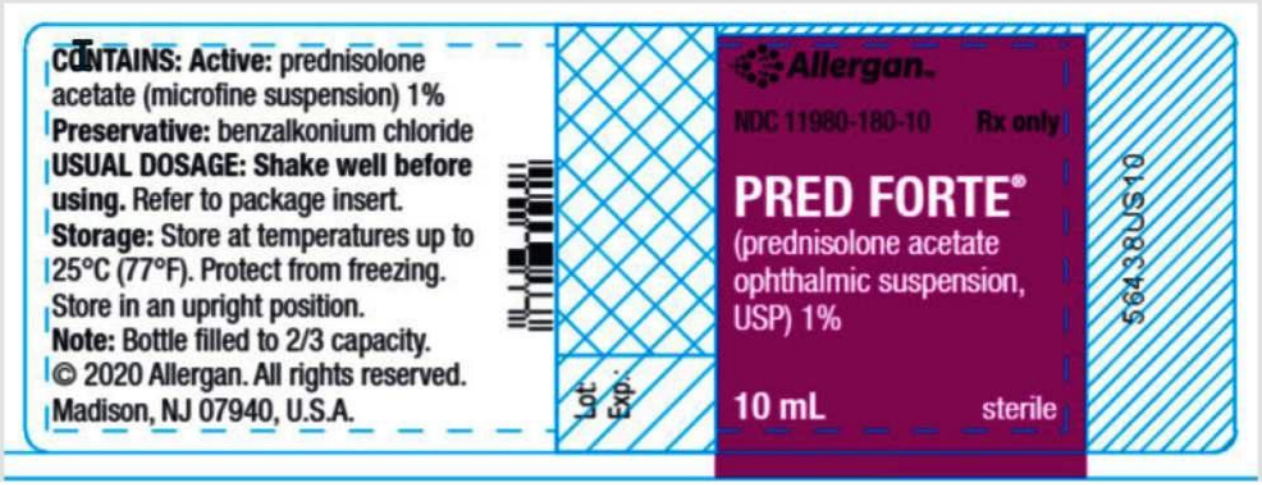
Deficiency Comments:

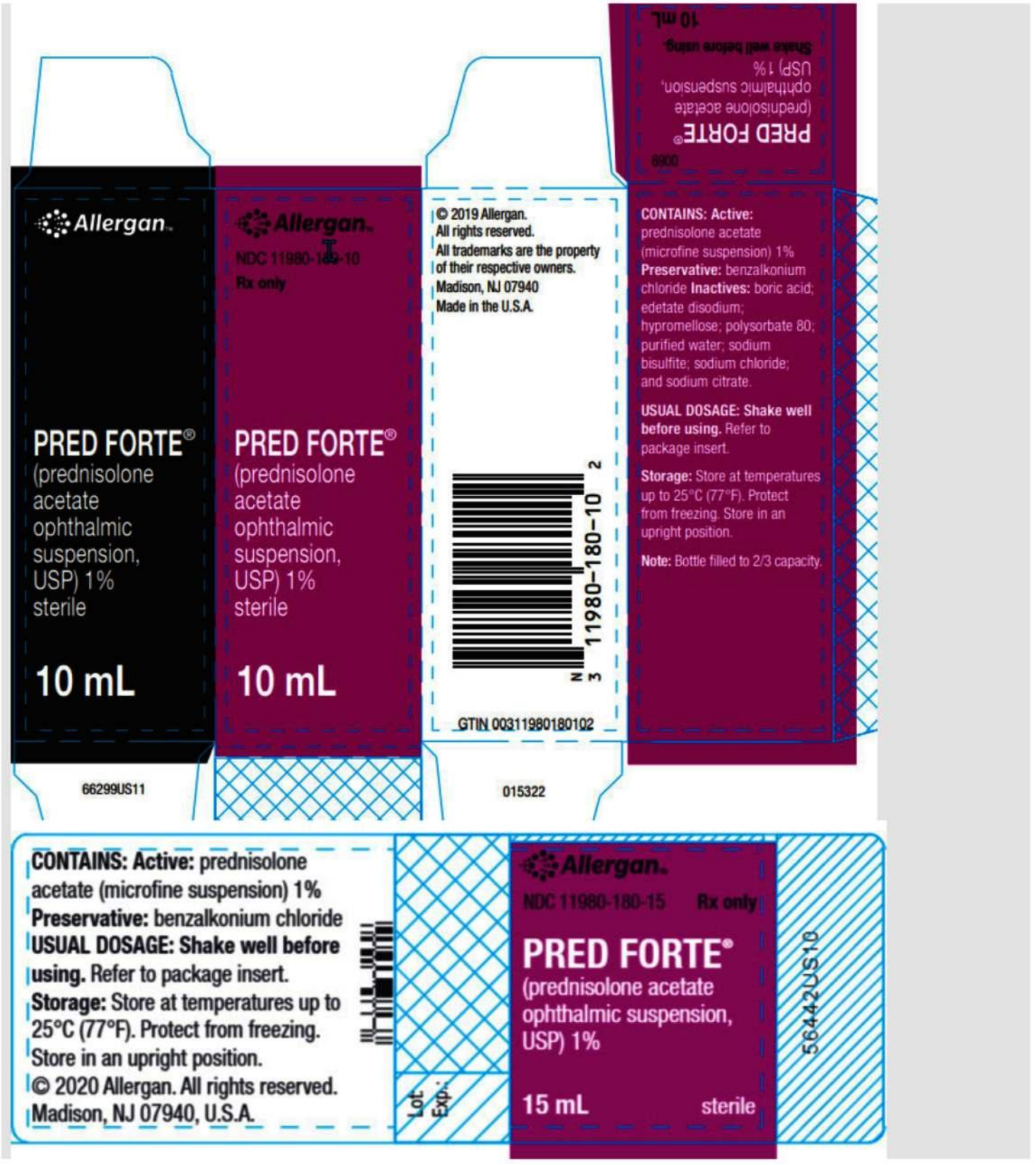
4.5 MODEL CONTAINER LABELS (C3)

Model container/carton/blister labels (Source: NDA 017011 AR-51, 06/28/2021 **)**




Allergan
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
sterile
5 mL
66210US11
Allergan
NDC 11980-180-05
Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
sterile
5 mL
© 2019 Allergan.
All rights reserved.
All trademarks are the property of their respective owners.
Madison, NJ 07940
Made in the U.S.A.
3 11980-180-05 8
GTIN 00311980180058
015318
CONTAINS: Active: prednisolone acetate (microfine suspension) 1% Preservative: benzalkonium chloride Inactives: boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate.
USUAL DOSAGE: Refer to package insert.
Shake well before using.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 1/2 capacity.
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
Shake well before using.
5 mL


CONTAINS: Active: prednisolone acetate (microfine suspension) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 2/3 capacity.
© 2020 Allergan. All rights reserved.
Madison, NJ 07940, U.S.A.
Lot:
Exp:
Allergan
NDC 11980-180-10 Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
10 mL sterile
564.38US10


Allergan
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
sterile
10 mL
Allergan
NDC 11980-180-10
Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
sterile
10 mL
© 2019 Allergan.
All rights reserved.
All trademarks are the property of their respective owners.
Madison, NJ 07940
Made in the U.S.A.
N 3 11980-180-10 2
GTIN 00311980180102
CONTAINS: Active: prednisolone acetate (microfine suspension) 1% Preservative: benzalkonium chloride Inactives: boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate.
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 2/3 capacity.
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
Shake well before using.
10 mL
66299US11
015322
CONTAINS: Active: prednisolone acetate (microfine suspension) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
© 2020 Allergan. All rights reserved.
Madison, NJ 07940, U.S.A.
Lot
Exp.
Allergan
NDC 11980-180-15 Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
15 mL sterile
56442US10

5 ASSESSMENT OF ANDA LABELING AND LABELS (C3)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C3)

5.1.1 DRUG PRODUCT REVIEW (C3)

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

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)? _____

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:

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

Assessment (R#01): [redacted] (b) (4)

If "No," explain.

For OTC Drugs and Controlled Substances:

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:

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None (R#01)

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

R#01: None

5.1.2 DESCRIPTION (C3)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	N/A

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Previous ANDA Labeling	Each mL of prednisolone acetate ophthalmic suspension USP contains: Active: prednisolone acetate (micronized) 1% Inactive: benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection. The pH during its shelf life ranges from 5.0 to 6.0.
Current ANDA Labeling	Each mL of prednisolone acetate ophthalmic suspension USP contains: Active: prednisolone acetate (micronized) 1% Inactive: benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection. The pH during its shelf life ranges from 5.0 to 6.0. Assessment: Acceptable - No change. There was no new Prescribing Information submitted this cycle.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C3)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	N/A
Previous ANDA Labeling	HOW SUPPLIED Prednisolone acetate ophthalmic suspension USP, 1% is supplied sterile in opaque white bottle with opaque white nozzle with pink cap as follows: NDC 70748-332-02: 5 mL in 10 mL bottle NDC 70748-332-03: 10 mL in 15 mL bottle NDC 70748-332-04: 15 mL in 15 mL bottle Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.
Current ANDA Labeling	HOW SUPPLIED Prednisolone acetate ophthalmic suspension USP, 1% is supplied sterile in opaque white bottle with opaque white nozzle with pink cap as follows: NDC 70748-332-02: 5 mL in 10 mL bottle NDC 70748-332-03: 10 mL in 15 mL bottle NDC 70748-332-04: 15 mL in 15 mL bottle Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position. Assessment: Acceptable - No change. There was no new Prescribing Information submitted this cycle.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C3)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements
Previous ANDA Labeling

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address on ANDA Prescribing Information	Manufactured for: **Lupin Pharmaceuticals, Inc.** Baltimore, Maryland 21202 United States. Manufactured by: **Lupin Limited** Pithampur (M. P.) - 454 775 India. Revised: April 2022
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured for: **Lupin Pharmaceuticals, Inc.** Baltimore, Maryland 21202 United States. Manufactured by: **Lupin Limited** Pithampur (M. P.) - 454 775 India. Revised: April 2022 Assessment: Acceptable - No change. There was no new Prescribing Information submitted this cycle.

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

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C3)

Reviewer Assessment:

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

5.2.1 OPHTHALMIC PRODUCTS (C3)

Reviewer Assessment:

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

Deficiency	No Deficiency	
☐	☒	Name of all **inactive ingredients** are listed appropriately.
☐	☒	Tamper evident (ophthalmic products) requirements are met.
☐	☒	**Image of eye and statement** is appropriately shown on product label.

Reviewer Comments:

(b) (4)

(b) (4)

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Unit-Dose Carton expression of strength** appropriately stated.
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The carton labeling is adequate. The carton labeling submitted this cycle did not contain any changes to (b) (4) the labeling. (b) (4)

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☒ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	**Dosage form, pharmacologic/therapeutic class, and route** of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and[21 CFR 201.57(c)(12)(i)(E)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine,

Deficiency	No Deficiency	
		enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(j)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing information meets **formatting requirements** [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The Prescribing Information is adequate. There was no new Prescribing Information submitted this cycle, it was found adequate in the prior cycle and remains so.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C3)

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

Reviewer Assessment:

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

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

Reviewer Comments:

Deficiency Comments:

Andrew D Tran

Digitally signed by Andrew D Tran
Date: 1/16/2024 10:30:46AM
GUID: 6387aced004e24ebb3dc5aaff00896ef

Marshall Florence

Digitally signed by Marshall Florence
Date: 1/16/2024 11:29:35AM
GUID: 55eefa420051b501ac3ced124279f785

Labeling Review

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

Date of This Review	10/31/2022
ANDA Number(s)	216935
Review Number	2
Applicant Name	Lupin Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Prednisolone Acetate Ophthalmic Suspension USP, 1%
Proposed Proprietary Name	N/A
Submission Received Date	September 02, 2022
Primary Labeling Reviewer	Michael Evans
Secondary Labeling Reviewer	Marshall Florence

Review Conclusion

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

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

TABLE OF CONTENTS

1 LABELING COMMENTS (C2)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C2)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C2)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received September 02, 2022.

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

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 (C2)

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

2 INSTRUCTIONS FOR ASSESSMENT (C2)

General Comments:

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

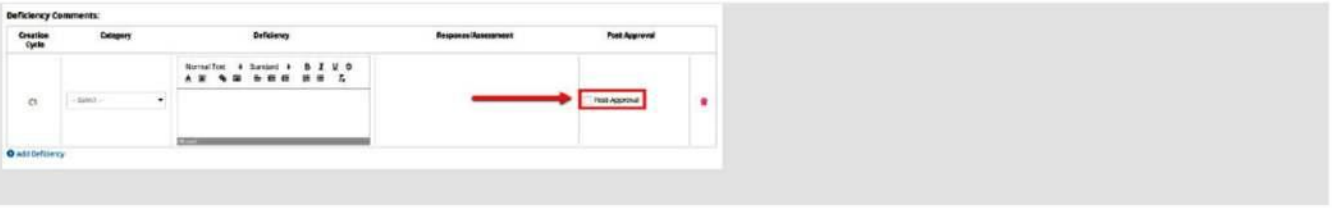
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

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

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

Deficiency Comments:

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



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C2)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	5 mL, 10 mL and 15 mL bottles	09/02/2022	Satisfactory
Blister	N/A	N/A		
Carton	Draft	One per carton	09/02/2022	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: September 2022	09/02/2022	Satisfactory
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C2)

4.1 REGULATORY INFORMATION (C2)

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

4.2 MODEL PRESCRIBING INFORMATION (C2)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**
(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
NDA#/Supplement# (S-000 if original): NDA017011 / S-050 **Supplement Approval Date:** 06/06/2018 **Proprietary Name:** PRED FORTE **Established Name:** Prednisolone Acetate Ophthalmic Suspension **Description of Supplement:** This Prior Approval supplemental new drug application provides for the addition of "eye pain" to the **ADVERSE REACTIONS** section of the Package Insert. **CMC S-051, approved 06/19/2020 - CBE changing cap color from white to pink** **CMC S-052 and S-053** does not affect labeling **Link:** https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4274208_3853476_090140af8049e7fe_NDA017011_2689668
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: The prescribing information is current with the RLD with minor revisions required **Deficiency Comments:**		

4.3 PATENTS AND EXCLUSIVITIES (C2)

The Orange Book was searched on 10/31/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA017011) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
	N/A						

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

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

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

4.4 UNITED STATES PHARMACOPEIA (USP) (C2)

The USP was searched on 10/31/2022

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Prednisolone Acetate Ophthalmic Suspension	Packaging and storage—Preserve in tight containers.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

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

4.5 MODEL CONTAINER LABELS (C2)

Model container/carton/blister labels (Source: AR-51, 06/28/2021)

CONTAINS: **Active:** prednisolone acetate (microfine suspension) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position. **Shake well before using.**
Note: Bottle filled to 1/2 capacity.
© 2020 Allergan. Madison, NJ 07940, U.S.A.

Lot:
Exp.:

Allergan
NDC 11980-180-05 Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
5 mL sterile

56388US10

CONTAINS: **Active:** prednisolone acetate (microfine suspension) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 2/3 capacity.
© 2020 Allergan. All rights reserved.
Madison, NJ 07940, U.S.A.

Lot:
Exp.:

Allergan
NDC 11980-180-10 Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
10 mL sterile

56438US10


Allergan
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1% sterile
10 mL
66299US11
Allergan
NDC 11980-180-10
Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1% sterile
10 mL
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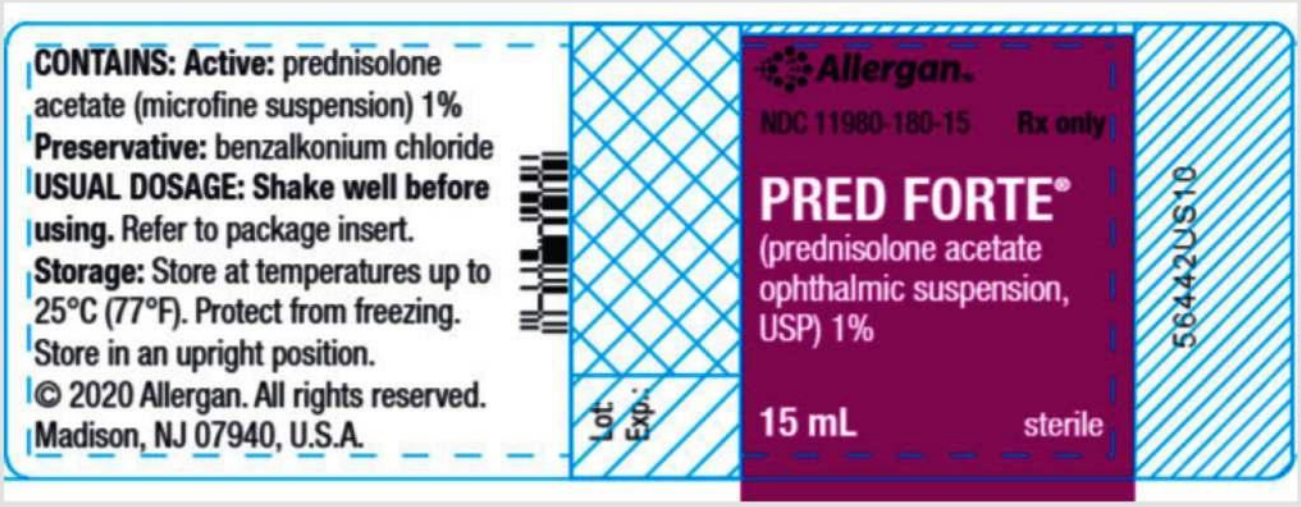
All trademarks are the property of their respective owners.
Madison, NJ 07940
Made in the U.S.A.
N 3 11980-180-10 2
GTIN 00311980180102
015322
CONTAINS: Active: prednisolone acetate (microfine suspension) 1% Preservative: benzalkonium chloride Inactives: boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate.
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 2/3 capacity.
0069
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
Shake well before using.
10 mL


CONTAINS: Active: prednisolone acetate (microfine suspension) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
© 2020 Allergan. All rights reserved.
Madison, NJ 07940, U.S.A.
Lot
Exp.
Allergan
NDC 11980-180-15 Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
15 mL sterile
56442US10

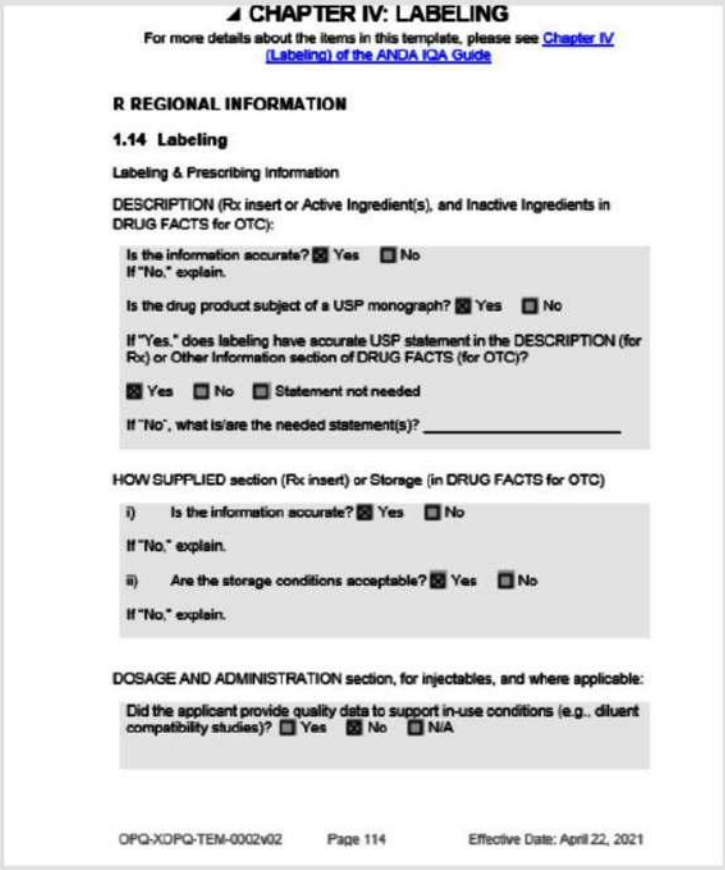
5 ASSESSMENT OF ANDA LABELING AND LABELS (C2)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C2)

5.1.1 DRUG PRODUCT REVIEW (C2)

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

08/26/2022 (not archived)



CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the ANDA IQA Guide

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)? _____

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

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

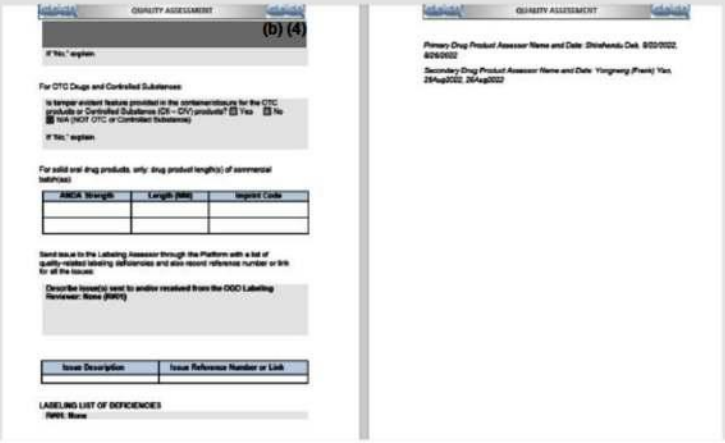
ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

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

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

OPQ-XOPQ-TEM-0002v02 Page 114 Effective Date: April 22, 2021



QUALITY ASSESSMENT

(b) (4)

If "No," explain

For OTC Drugs and Controlled Substances

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 bottle(size)

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:

Describe Issue(s) sent to and/or received from the OGD Labeling Reviewer: None (RWR)

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES
RWR: None

QUALITY ASSESSMENT

Primary Drug Product Assessor Name and Date: Dhirbendu Deb, 8/26/2022

Secondary Drug Product Assessor Name and Date: Yongneng (Frank) Yao, 26Aug2022, 26Aug2022

5.1.2 DESCRIPTION (C2)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL of **PRED FORTE®** contains: **Active:** prednisolone acetate (microfine suspension) 1% **Inactives**: benzalkonium chloride as preservative; boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate. The pH during its shelf life ranges from 5.0 - 6.0.

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Previous ANDA Labeling	Each mL of prednisolone acetate ophthalmic suspension USP contains: **Active:** prednisolone acetate (micronized) 1% **Inactive:** benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection. The pH during its shelf life ranges from 5.0 to 6.0. ***It is noted in the formulation (micronized) per Bioequivalence review is adequate as of 07/21/2022.***
Current ANDA Labeling	Each mL of prednisolone acetate ophthalmic suspension USP contains: **Active:** prednisolone acetate (micronized) 1% **Inactive:** benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection. The pH during its shelf life ranges from 5.0 to 6.0. **Assessment**: Acceptable - No change

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C2)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**HOW SUPPLIED** **PRED FORTE®** (prednisolone acetate ophthalmic suspension, USP) 1% is supplied sterile in opaque white LDPE plastic bottles with droppers with white high impact polystyrene (HIPS) caps as follows: 1 mL in 5 mL bottle - NDC 11980-180-01 5 mL in 10 mL bottle - NDC 11980-180-05 10 mL in 15 mL bottle - NDC 11980-180-10 15 mL in 15 mL bottle - NDC 11980-180-15 Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position. **PLEASE NOTE THE RLD NDA CMC S-051 changes the white cap to a pink cap to follow AAO guidelines**
Previous ANDA Labeling	(b) (4) [redacted]

Table 8: Comparison of Model Labeling to ANDA Labeling	
	[redacted] (b) (4)
Current ANDA Labeling	**HOW SUPPLIED** Prednisolone acetate ophthalmic suspension USP, 1% is supplied sterile in opaque white bottle with opaque white nozzle with pink cap as follows: NDC 70748-332-02: 5 mL in 10 mL bottle NDC 70748-332-03: 10 mL in 15 mL bottle NDC 70748-332-04: 15 mL in 15 mL bottle Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position. **Assessment**: Acceptable - [redacted] (b) (4) . Please note RLD's current PI from AT-52 **RLD per AR - 52, 06/30/2022** **HOW SUPPLIED** **PRED FORTE®** (prednisolone acetate ophthalmic suspension, USP) 1% is supplied sterile in opaque white LDPE plastic bottles with droppers with pink high impact polystyrene (HIPS) caps as follows: 1 mL in 5 mL bottle - NDC 11980-180-01 5 mL in 10 mL bottle - NDC 11980-180-05 10 mL in 15 mL bottle - NDC 11980-180-10 15 mL in 15 mL bottle - NDC 11980-180-15 **Storage:** Store at up to 25°C (77°F). Protect from freezing. Store in an upright position. **Revised: 05/2020** Distributed by: Allergan USA, Inc. Madison, NJ 07940 © 2020 Allergan. All rights reserved. All trademarks are the property of their respective owners. v1.2USPI180 71592US14

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C2)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements
Previous ANDA Labeling

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address on ANDA Prescribing Information	Manufactured for: **Lupin Pharmaceuticals, Inc.** Baltimore, Maryland 21202 United States. Manufactured by: **Lupin Limited** Pithampur (M. P.) - 454 775 India. Revised: April 2022
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured for: **Lupin Pharmaceuticals, Inc.** Baltimore, Maryland 21202 United States. Manufactured by: **Lupin Limited** Pithampur (M. P.) - 454 775 India. Revised: September 2022 **Assessment:** Acceptable - No change

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**
Manufactured by: Lupin Limited Pithampur (M. P.) - 454 775 India. Revised: April 2022	Manufactured for: Lupin Pharmaceuticals, Inc. Baltimore, Maryland 21202 United States.		

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C2)

Reviewer Assessment:

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

Reviewer Comments:

This review

The applicant has made the requested revisions to the container labels, and they are acceptable.

C1 review

The container labels are inadequate

It is noted that the applicant has followed the FDA Tall Man lettering scheme for prednisoLONE.

prednisoLONE

(b) (4)

[redacted] (b) (4)

[redacted].

Deficiency Comments:

Deficiency # 1 [redacted] (b) (4)

Created in C1 [redacted]

Container Label
Response / Assessment: Acceptable

Deficiency # 2 [redacted] (b) (4)

Created in C1

Container Label
Response / Assessment: Acceptable

5.2.1 OPHTHALMIC PRODUCTS (C2)

Reviewer Assessment:

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

Reviewer Comments:

This review

The applicant has revised the cap color to pink as requested in order to follow cap color AAO guidelines. The applicant has also clarified that shrink wrap show tamper evidence. This is acceptable.

3.2.P.7, 10/07/2022

(b) (4)

C1 review

The bottles qualify for the too small exemption where only the preservative is listed as does the RLD. The inactive ingredients are listed on the carton correctly.

(b) (4).

The AAO recommends a pink cap

(b) (4)

Refer to section 4.2 where RLD NDA **CMC S-051, approved 06/19/2020 - CBE changing cap color from white to pink**

Deficiency Comments:

Deficiency # 1 Created in C1 Container Label Response / Assessment:	Ensure that the cap color of your drug product is pink so that it follows the American Academy of Ophthalmology (AAO) packaging color-coding scheme. Refer to the American Academy of Ophthalmology (AAO) packaging color-coding. Acceptable
Deficiency # 2 Created in C1 Container Label Response / Assessment:	Ensure that your drug product follows the tamper-evident requirements for ophthalmic preparations. Refer to 21 CFR 200.50(a)(3). **Acceptable -** We wish to inform the Agency that as per 21 CFR 200.50(a)(3), we have used transparent shrink sleeves with the text printed as "PROTECTIVE SEAL" for Tamper Evidence which should be peeled or torn off completely upon first opening of the eye drop bottle

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

This review

The applicant has made the requested revisions to the carton labels, and they are acceptable.

C1 review

The carton label is inadequate.

(b) (4)

The carton label has a graphical representation of the eye on the PDP which is an allowable difference.

Deficiency Comments:
Deficiency # 1 [redacted] (b) (4)

Created in C1

Carton Labeling
Response / Assessment: Acceptable

5.4 PRESCRIBING INFORMATION (C2)

Reviewer Assessment:

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

Reviewer Comments:

This review

The applicant has made the requested revisions and the prescribing information is acceptable.

C1 review

The prescribing information is current with the RLD. The PI requires minor editorial revisions.
Please not the cap color should be PINK.

Deficiency Comments:

Deficiency # 1 Created in C1 Prescribing Information Response / Assessment:	Reduce the title to title case so that it reads as: **"Prednisolone Acetate Ophthalmic Suspension USP,1%"**. Acceptable
Deficiency # 2 Created in C1 Prescribing Information Response / Assessment:	(b) (4) Acceptable

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C2)

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

Reviewer Assessment:

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

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

Reviewer Comments:

Deficiency Comments:

Michael Evans

Digitally signed by Michael Evans
Date: 11/14/2022 11:25:52AM
GUID: 5473743d0009393d289decf0b8b5e69e

Marshall Florence

Digitally signed by Marshall Florence
Date: 11/14/2022 02:42:11PM
GUID: 55eefa420051b501ac3ced124279f785

Labeling Review

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

Date of This Review	07/27/2022
ANDA Number(s)	216935
Review Number	1
Applicant Name	Lupin Limited
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Prednisolone Acetate Ophthalmic Suspension USP, 1%
Proposed Proprietary Name	N/A
Submission Received Date	April 11, 2022
Primary Labeling Reviewer	Michael Evans
Secondary Labeling Reviewer	Marshall Florence

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

*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
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submission received April 11, 2022 :

1. CONTAINER LABEL
   a. Ensure that the cap color of your drug product is pink so that it follows the American Academy of Ophthalmology (AAO) packaging color-coding scheme. Refer to the American Academy of Ophthalmology (AAO) packaging color-coding.
   b. Ensure that your drug product follows the tamper-evident requirements for ophthalmic preparations. Refer to 21 CFR 200.50(a)(3).
   c. (b) (4) .
   d. (b) (4)

2. CARTON LABELING
   (b) (4)

3. PRESCRIBING INFORMATION
   a. Reduce the title. to title case so that it reads as: "**Prednisolone Acetate Ophthalmic Suspension USP,1%**".
   b. (b) (4)

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

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

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

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

1.3 POST-APPROVAL REVISIONS

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

2 INSTRUCTIONS FOR ASSESSMENT

General Comments:

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

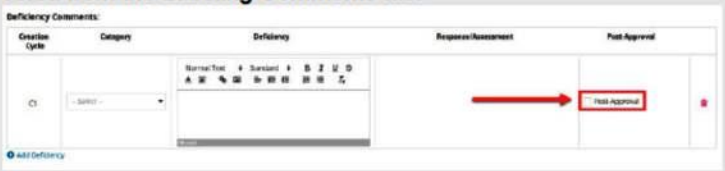
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

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

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

Deficiency Comments:

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



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

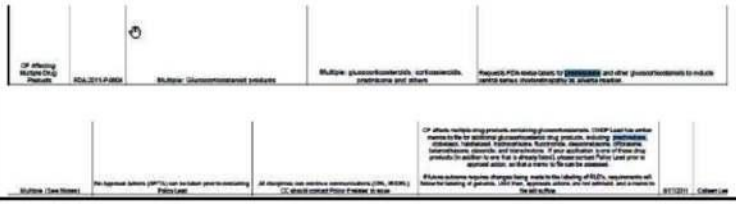
Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	5 mL, 10 mL and 15 mL bottles	04/11/2022	Revise
Blister	N/A	N/A		
Carton	Draft	One per carton	04/11/2022	Revise

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: April 2022	04/11/2022	Revise
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		

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

4 LABELING REVIEW INFORMATION

4.1 REGULATORY INFORMATION

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

4.2 MODEL PRESCRIBING INFORMATION

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** NDA017011 / S-050 **Supplement Approval Date:** 06/06/2018 **Proprietary Name:** PRED FORTE **Established Name:** Prednisolone Acetate Ophthalmic Suspension **Description of Supplement:** This Prior Approval supplemental new drug application provides for the addition of "eye pain" to the **ADVERSE REACTIONS** section of the Package Insert. **CMC S-051, approved 06/19/2020 - CBE changing cap color from white to pink** **CMC S-052 and S-053** does not affect labeling **Link:** https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4274208_3853476_090140af8049e7fe_NDA017011_2689668
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING
☐ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

Reviewer Assessment:

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

Reviewer Comments:
The prescribing information is current with the RLD with minor revisions required

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 07/27/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA017011) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

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

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

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
	N/A					

Reviewer Assessment:

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

Reviewer Comments:

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 07/27/2022

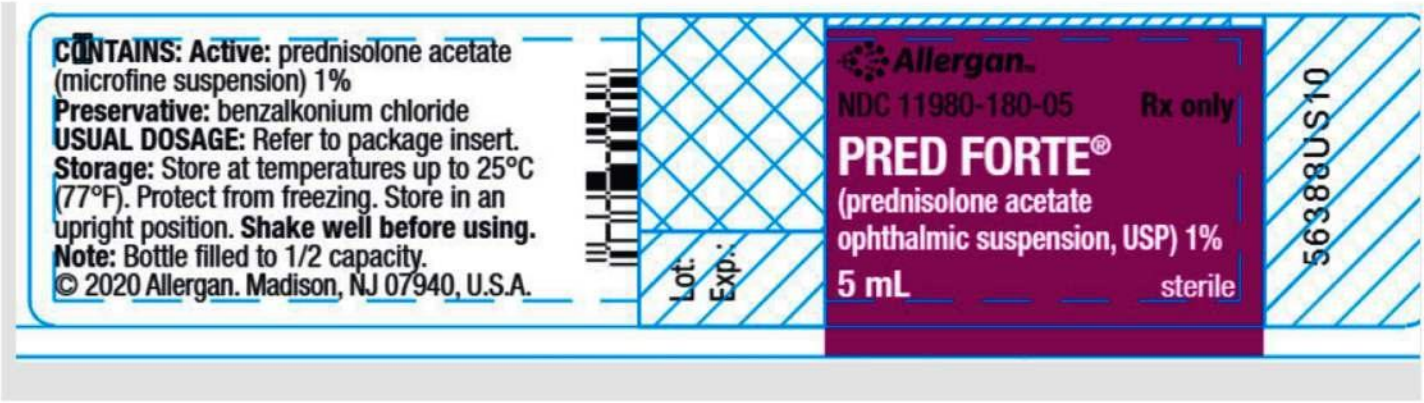
Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	Yes		Prednisolone Acetate Ophthalmic Suspension	Packaging and storage—Preserve in tight containers.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

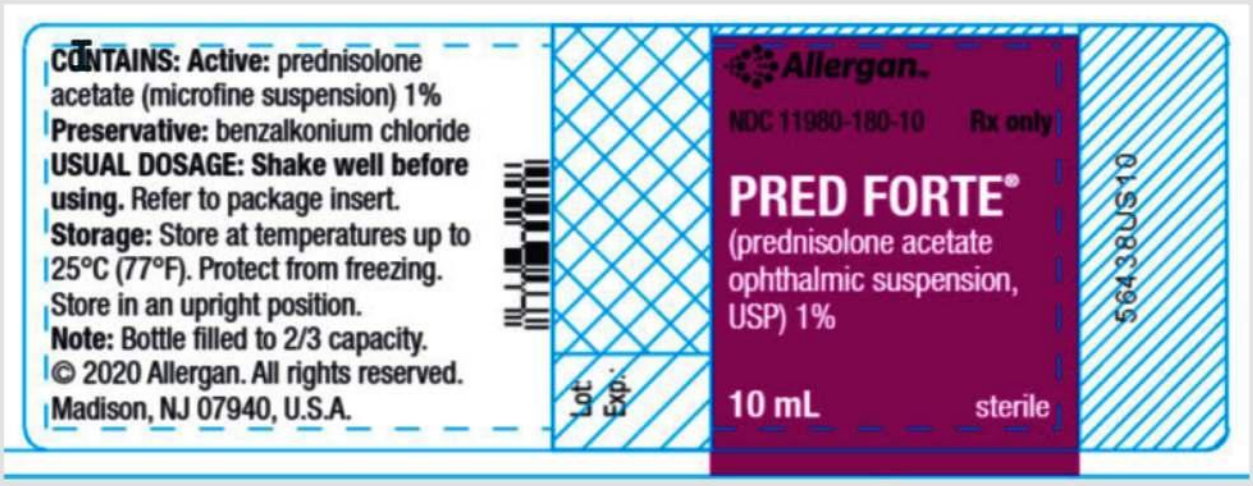
Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.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

4.5 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: AR-51, 06/28/2021 **)**




Allergan
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
sterile
5 mL
Allergan
NDC 11980-180-05
Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
sterile
5 mL
© 2019 Allergan.
All rights reserved.
All trademarks are the property of their respective owners.
Madison, NJ 07940
Made in the U.S.A.
N 3 11980-180-05 8
GTIN 00311980180058
CONTAINS: Active: prednisolone acetate (microfine suspension) 1% Preservative: benzalkonium chloride Inactives: boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate.
USUAL DOSAGE: Refer to package insert.
Shake well before using.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 1/2 capacity.
66210US11
015318
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
5 mL
Shake well before using.


CONTAINS: Active: prednisolone acetate (microfine suspension) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 2/3 capacity.
© 2020 Allergan. All rights reserved.
Madison, NJ 07940, U.S.A.
Lot:
Exp:
Allergan
NDC 11980-180-10
Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
10 mL
sterile
56438US10


Allergan
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
sterile
10 mL
Allergan
NDC 11980-180-10
Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
sterile
10 mL
66299US11
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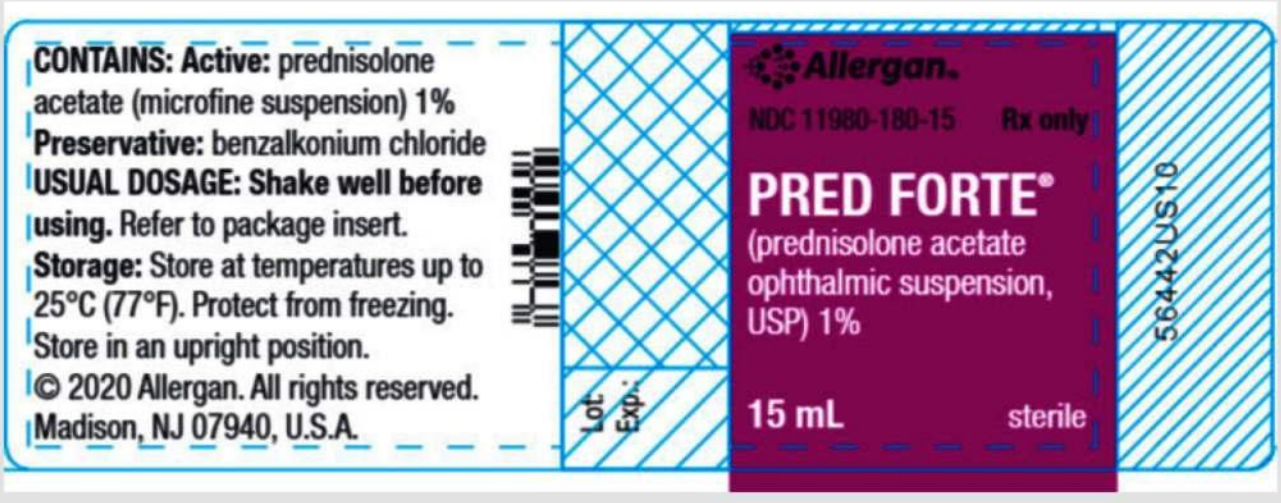
All rights reserved.
All trademarks are the property of their respective owners.
Madison, NJ 07940
Made in the U.S.A.
N 3 11980-180-10 2
GTIN 00311980180102
015322
CONTAINS: Active: prednisolone acetate (microfine suspension) 1% Preservative: benzalkonium chloride Inactives: boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate.
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
Note: Bottle filled to 2/3 capacity.
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
Shake well before using.
10 mL


CONTAINS: Active: prednisolone acetate (microfine suspension) 1%
Preservative: benzalkonium chloride
USUAL DOSAGE: Shake well before using. Refer to package insert.
Storage: Store at temperatures up to 25°C (77°F). Protect from freezing. Store in an upright position.
© 2020 Allergan. All rights reserved.
Madison, NJ 07940, U.S.A.
Lot:
Exp.:
Allergan
NDC 11980-180-15 Rx only
PRED FORTE®
(prednisolone acetate ophthalmic suspension, USP) 1%
15 mL sterile
56442US10

5 ASSESSMENT OF ANDA LABELING AND LABELS

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

5.1.1 DRUG PRODUCT REVIEW

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

DP review has not been started or not available in Platform.

5.1.2 DESCRIPTION

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL of **PRED FORTE®** contains:

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	Active: prednisolone acetate (microfine suspension) 1% **Inactives**: benzalkonium chloride as preservative; boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate. The pH during its shelf life ranges from 5.0 - 6.0.
Previous ANDA Labeling	N/A
Current ANDA Labeling	Each mL of prednisolone acetate ophthalmic suspension USP contains: **Active:** prednisolone acetate (micronized) 1% **Inactive:** benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection. The pH during its shelf life ranges from 5.0 to 6.0. ***It is noted in the formulation (micronized) per Bioequivalence review is adequate as of 07/21/2022.***

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**HOW SUPPLIED** **PRED FORTE®** (prednisolone acetate ophthalmic suspension, USP) 1% is supplied sterile in opaque white LDPE plastic bottles with droppers with white high impact polystyrene (HIPS) caps as follows: 1 mL in 5 mL bottle - NDC 11980-180-01 5 mL in 10 mL bottle - NDC 11980-180-05 10 mL in 15 mL bottle - NDC 11980-180-10 15 mL in 15 mL bottle - NDC 11980-180-15 Storage: Store at up to 25°C (77°F). Protect from freezing. Store in an upright position. **PLEASE NOTE THE RLD NDA CMC S-051 changes the white cap to a pink cap to follow AAO guidelines**
Previous ANDA Labeling	N/A
Current ANDA Labeling	(b) (4) [redacted]

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	N/A
Name and Address on ANDA Container/Carton	N/A
Name and Address on ANDA Prescribing Information	N/A
Current ANDA Labeling	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	**01/21/2022** (b) (4) [redacted]
Name and Address on ANDA Container/Carton	**Containers** Manufactured by: **Lupin Limited** Pithampur (M.P.) 454 775, INDIA **Cartons** Manufactured for: **Lupin Pharmaceuticals, Inc.** Baltimore, Maryland 21202 United States Manufactured by: **Lupin Limited** Pithampur (M.P.) 454 775 INDIA

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address on ANDA Prescribing Information	Manufactured for: **Lupin Pharmaceuticals, Inc.** Baltimore, Maryland 21202 United States. Manufactured by: **Lupin Limited** Pithampur (M. P.) - 454 775 India. Revised: April 2022

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**
Manufactured by: Lupin Limited Pithampur (M. P.) - 454 775 India. Revised: April 2022	Manufactured for: Lupin Pharmaceuticals, Inc. Baltimore, Maryland 21202 United States.		

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

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].

Deficiency	No Deficiency	
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☒	☐	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The container labels are inadequate

It is noted that the applicant has followed the FDA Tall Man lettering scheme for prednisoLONE.

prednisoLONE

(b) (4)

Deficiency Comments:

Deficiency # 1

(b) (4)

Created in C1

Container Label

Response / Assessment:

Deficiency # 2

(b) (4)

Created in C1

Container Label

Response / Assessment:

5.2.1 OPHTHALMIC PRODUCTS

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	Ophthalmic product **cap colors** match the American Academy of Ophthalmology (AAO) packaging color-coding scheme.
☐	☒	Name and quantity (or proportion) of all **inactive ingredients** are listed appropriately.

Deficiency	No Deficiency	
☒	☐	Tamper evident (ophthalmic products) requirements are met.

Reviewer Comments:
The bottles qualify for the too small exemption where only the preservative is listed as does the RLD. The inactive ingredients are listed on the carton correctly.
There is no mention of this product being tamper evident. DLR will request clarification.
The AAO recommends a pink cap

Anti-inflammatory, steroids	Pink	197

Refer to section 4.2 where RLD NDA **CMC S-051, approved 06/19/2020 - CBE changing cap color from white to pink**

Deficiency Comments:

Deficiency # 1 Created in C1 Container Label Response / Assessment:	Ensure that the cap color of your drug product is pink so that it follows the American Academy of Ophthalmology (AAO) packaging color-coding scheme. Refer to the American Academy of Ophthalmology (AAO) packaging color-coding.
Deficiency # 2 Created in C1 Container Label Response / Assessment:	Ensure that your drug product follows the tamper-evident requirements for ophthalmic preparations. Refer to 21 CFR 200.50(a)(3).

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The carton label is inadequate.

[redacted] (b) (4)

The carton label has a graphical representation of the eye on the PDP which is an allowable difference.

Deficiency Comments:
Deficiency # 1 [redacted] (b) (4)

Created in C1

Carton Labeling
Response / Assessment:

5.4 PRESCRIBING INFORMATION

Reviewer Assessment:

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

Deficiency	No Deficiency	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The prescribing information is current with the RLD. The PI requires minor editorial revisions.
Please not the cap color should be PINK.

Deficiency Comments:

Deficiency # 1 Created in C1 Prescribing Information Response / Assessment:	Reduce the title, to title case so that it reads as: **"Prednisolone Acetate Ophthalmic Suspension USP,1%"**.
Deficiency # 2 Created in C1 Prescribing Information Response / Assessment:	(b) (4) [redacted]

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

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

Reviewer Assessment:

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

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

Reviewer Comments:

Deficiency Comments:

Michael Evans

Digitally signed by Michael Evans
Date: 8/24/2022 07:38:06AM
GUID: 5473743d0009393d289decf0b8b5e69e

Marshall Florence

Digitally signed by Marshall Florence
Date: 8/24/2022 07:57:49AM
GUID: 55eefa420051b501ac3ced124279f785

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216935

CHEMISTRY REVIEW(s)

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	216935
Review Cycle #	03
Applicant Name	Lupin Limited
Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP
Dosage Form. (click (+) for more than one)	Suspension
Proposed Strength(s)	1%
Route of Administration (click (+) for more than one)	Ophthalmic
Maximum Daily Dose	(b) (4)
Rx/OTC Dispensed	Rx
Proposed Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Drug Product Description	Prednisolone acetate ophthalmic suspension USP, 1% is a sterile, topical anti-inflammatory agent for ophthalmic use. Each mL of prednisolone acetate ophthalmic suspension USP contains: **Active:** prednisolone acetate (micronized) 1% **Inactive:** benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection. The pH during its shelf life ranges from 5.0 to 6.0.
Co-packaged product information	None
Device information, if any:	None

Storage Temperature/ Conditions	Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Shirshendu Deb	Yili Li
	Drug Product/ Labeling	Shirshendu Deb	Yili Li
	Manufacturing	Yuesheng Ye	Aditi Thakur
	Biopharmaceutics	Parnali Chatterjee	
	Microbiology	Ryan Blower	Bethanie Lee
	Other (specify):		
	RBPM	Christina Pleas	
	ATL	Yili Li	
Consults	**Discipline Consulted**	**Recommendation**	**Date**
	None		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
New ANDA SD 2	04/11/2022	All
Response to IR SD 4	07/28/2022	Quality
Response to IR SD 5	08/26/2022	Quality
Response to DRL SD 9	10/07/2022	Quality
Resubmission SD 10	10/17/2023	DP, Manufacturing
Response to IR SD 11	01/05/2024	BioPharm
CR response SD 12	05/10/2024	Quality

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Prednisolone Acetate, USP	AQ	07/09/2024	Per DMF Chemistry R#03, Yongjun Gao
	III		(b) (4)	N/A		Referenced in multiple approved ANDA and/or NDA including suspension (A064065)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N203491)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N021373)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A064135)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A210765)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N019845)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A065307)
	III					Referenced in multiple approved ANDA and/or NDA (A206716-powder, for solution)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A212450)

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N017011	Drug Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL Approval Date: Approved Prior to Jan 1, 1982

ANDA	N/A	No approved ANDA for prednisolone acetate ophthalmic suspension is currently active.

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

Overall Quality Deficiencies - None

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The ANDA is recommended for CMC approval because all discipline reviews are adequate. This is not an NDSRI impact application.

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Comments:

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA-216935-ORIG-1-AMEND-12
Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP (5mL, 10mL, 15mL)
Strengths	1%
Dosage Form	Suspension
Administration Route	Ophthalmic
Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Applicant Name	Lupin Limited
RLD Number	N017011
Primary Assessor	
Secondary Assessor	

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Inadequate - Minor → Adequate

Assessment Summary:

Facilities: Withhold is recommended due to unacceptable OAI compliance status of both the DS and DP manufacturing sites due to GMP inspections results.

Pre-approval inspection of the Lupin (FEI: 3007549629) (b) (4) manufacturing facility is also needed once the compliance status is resolved. The facility does not have a history of manufacturing suspensions. The other facilities (lab testing sites) proposed are acceptable.

Process: Withhold is recommended. The risks of the proposed manufacturing operations are not fully mitigated by the development data, exhibit batch data, and process controls. (b) (4)

Product Description:

1.0 DESCRIPTION OF DOSAGE FORM

Table 1: Description of the Drug Product

Fill Volume	Description
5 mL (b) (4) 10 mL round opaque white (b) (4) bottle)	White to off-white milky fine suspension filled in opaque white bottle closed with opaque white nozzle and then with white cap.
10 mL (b) (4) 15 mL round opaque white (b) (4) bottle)	
15 mL (b) (4) 15 mL round opaque white (b) (4) bottle)	

Dosage:

DOSAGE AND ADMINISTRATION

Shake well before using. Instill one to two drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased if necessary. Care should be taken not to discontinue therapy prematurely.

(b) (4)

Process Description:

(b) (4)

3.0 INTENDED COMMERCIAL BATCH MANUFACTURING RECORDS AND PACKAGING RECORDS

(b) (4)

Product	Fill Volume	Exhibit Batch Size	Intended Commercial Batch Size	Scale Up
Prednisolone Acetate Ophthalmic Suspension USP 1%	5 mL in 10 mL (b) (4) Bottle	(b) (4)		
	10 mL in 15 mL (b) (4) Bottle			
	15 mL in 15 mL (b) (4) Bottle			

Following intended commercial batch production records are provided under in this section.

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List Submissions being assessed (Table):

Document Description (SD #)	Date Received
PFC (SD 1)	01/21/2022
Original Submission (SD 2)	04/11/2022
Request for SEPT 14, 2022, Mid-Cycle Meeting (SD 3)	06/08/2022
Response to Micro IR (SD 5)	08/26/2022
Response to Quality IR (SD 9)	10/07/2022
Quality information (SD #0010)	10/17/2023
Quality information (SD #0011)	01/05/2024
Quality information (SD #0012)	05/10/2024

Additional Submissions:

Document Description (SD #)	Date Received
Response to Biopharm IR (SD 4)	07/28/2022
Response to Clinical IR (SD 6)	09/01/2022
Response to Labeling IR (SD 7)	09/02/2022
Response to Bioequivalence (SD 8)	09/19/2022

Highlight Key Issues from Last Cycle and Their Resolution:

- The applicant does not account for [redacted] (b) (4)
- [redacted] (b) (4) . Additional process development data may be required.
- Surveillance inspections found [redacted] (b) (4) and [redacted] (b) (4) Lupin Limited (FEI: 3007549629), manufacturing facilities to be unacceptable.

Amendment review (ANDA-216935-ORIG-1-AMEND-10):

[redacted] (b) (4)

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

Amendment review (ANDA-216935-ORIG-1-AMEND-12):

No outstanding deficiency according to the secondary reviewer(s) and supervisor.

List Number of Comparability Protocols:

1. Lifecycle Management Considerations

Post-approval inspection?	Yes. #PoAI. Facility Name/FEI: M/s. Lupin Limited/#3007549629
Lifecycle considerations	Yes (#Lifecycle)
[redacted] (b) (4)	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
[redacted] (b) (4)			Approve - Based on Previous History
[redacted] (b) (4)			Approve - Based on Previous History
M/s. Lupin Limited [redacted] (b) (4)	3007549629	[redacted] (b) (4)	Approve - Based on

(b) (4)			Previous History (Refer to the previous review for more details)
M/s. Lupin Limited Unit-3, Plot No. M-1 and M-3-A, Special Economic Zone, Phase – II, Misc. Zone Apparel Park,, Pithampur, Madhya Pradesh,	3009107538	(b) (4)	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History

II. Drug Product Manufacturing

(b) (4)

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1. List of Testing Facilities

(b) (4)
. The facilities proposed below, unless noted otherwise, are within compliance standards and have the ability to perform the function and responsibilities outline in the application following assessment:

Facility Name/FEI	Responsibilities	Previous OPMA evaluation (Link)
(b) (4)		Relevant and acceptable.
M/s. Lupin Limited FEI: 3009107538	(b) (4) 2018 inspection covered laboratory operations. The current compliance status is acceptable.	Relevant and acceptable.
(b) (4)		Relevant and acceptable.

2. Facility Level Evaluation of Commercial DS/DP Testing Facility

Facility name/FEI	
Facility experience	Choose an item.
Quality oversight	Choose an item.
Data concerns	Choose an item.

PAI / 704(a)(4)	Choose an item.
Facility Status Assessment: Choose an Item	

3. Facility Level Evaluation of Primary Packaging Facility

Facility name/FEI	
Process experience	Choose an item.
Quality oversight	Choose an item.
Quality defect signals	Choose an item.
PAI / 704(a)(4)	Choose an item.
Facility Status Assessment: Choose an Item	

4. Pre-Approval Inspection / 704(a)(4) Summary

Facility name/FEI	
Inspection / 704 (a)(4) Request dates	
Assessor participated in PAI?	Choose an item.
Issues identified and PAI / 704(a)(4) resolution	
Request for Additional Information (#RAI) and Response	
Outcome	Choose an item.

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
• None (refer to secondary reviewer(s)/supervisor).

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Andrew Idzior	Sateesh Sathigari	9/5/2022	IR	Withheld
2	Andrew Idzior	Sateesh Sathigari	11/7/2022	CR Minor	Withheld
3	Yuesheng Ye	N. Chidambaram, Ph.D.	3/15/2024	CR Minor	Approve
4	Yuesheng Ye	Kejun Cheng, Ph.D.	7/19/2024	CR Minor → Adequate	Approve

Kejun Cheng

Digitally signed by Kejun Cheng
Date: 7/24/2024 12:13:10PM
GUID: 53161750000085bec5cec837d47498f0

Yuesheng Ye

Digitally signed by Yuesheng Ye
Date: 7/24/2024 05:18:33PM
GUID: 5203e2c70001f9a26cd12224ab5f697d

ANDA 216935
Assessment R03

Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP
Dosage Form	Suspension
Strength	1%
Route of Administration	Ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Lupin Limited
US agent, if applicable	Ms. Kalpana Vanam [Senior Vice President, Regulatory Affairs] Lupin Pharmaceuticals, Inc., 400 Campus Drive, Somerset, NJ 08873 US Agent DUNS: (b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001	01-21-2022	All
0002	04-11-2022	All
0004	07-28-2022	Quality
0005	08-26-2022	Quality (3.2.P.3)
0009 (R01a)	10-07-2022	Quality (both DS & DP sections)
0010 (R02)	10-17-2023	Quality
0011 (R02)	01-05-2024	Quality
0012 (R03)	05-10-2024	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance*		
Drug Product	Shirshendu Deb	Yongneng Yao (DRL), Yili Li
Manufacturing		
Microbiology		
Biopharmaceutics		
Regulatory Business Process Manager		
Application Technical Lead		
Laboratory (OTR)		
Environmental		

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Prednisolone Acetate, USP (b) (4)	AQ	07/09/2024	Per DMF Chemistry R#03, Yongjun Gao
	III			N/A		Referenced in multiple approved ANDA and/or NDA including suspension (A064065)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N203491)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N021373)
	III					Referenced in multiple approved ANDA and/or NDA

(b) (4)	(b) (4)			
				including suspension (A064135)
	III			Referenced in multiple approved ANDA and/or NDA including suspension (A210765)
	III			Referenced in multiple approved ANDA and/or NDA including suspension (N019845)
	III			Referenced in multiple approved ANDA and/or NDA including suspension (A065307)
	III			Referenced in multiple approved ANDA and/or NDA (A206716-powder, for solution)
	III			Referenced in multiple approved ANDA and/or NDA including suspension (A212450)

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N017011	Drug Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL Approval Date: Approved Prior to Jan 1, 1982
ANDA	N/A	No approved ANDA for prednisolone acetate ophthalmic suspension is currently active.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Proposed limits of NMT (b) (4) % are acceptable for each of the impurities: (b) (4)	3/18/2024	Vincent Crowley
CDRH				
Clinical				
Other				

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CHAPTER I: DRUG SUBSTANCE

For more details about the items in this template, please see Chapter I (Drug Substance) of the ANDA IQA Guide

Drug Substance Name	Prednisolone Acetate
ANDA Number	A216935
Applicant Name	Lupin Limited
Assessment Cycle Number	R03
DMF Number (if applicable)	(b) (4)
DMF Status	**Adequate**
DMF Holder	(b) (4)

Assessment Recommendation: **Adequate**

If Inadequate-Major, select Theme:

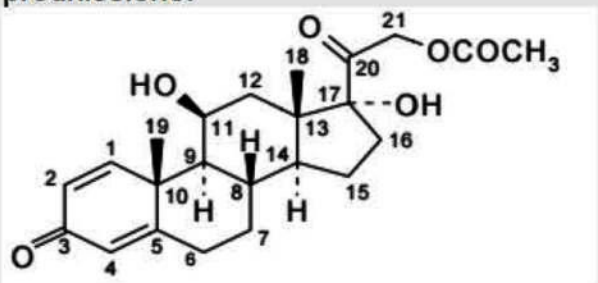
☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

If Inadequate-Major, enter Justification: *(Click link to view Justification Statements)*

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Prednisolone acetate is a compendial drug substance (CAS: 52-21-1) used to treat eye conditions due to inflammation or injury. The DS belongs to a synthetic glucocorticoid corticosteroid. It is the 21-acetate ester of prednisolone.



Therapeutic category: Indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

The molecular formula is $C_{23}H_{30}O_6$ and the molecular weight is 402.49 g/mol. The DS has poor water solubility but is soluble in organic solvents like chloroform, methanol, and ethanol. [redacted] (b) (4)

[redacted] (b) (4)

The firm referred to DMF [redacted] (b) (4) for information regarding the chemistry, manufacturing and controls used in the production of Prednisolone acetate, micronized. The DMF review is IQ-Minor (Reviewer Yongjun Gao)

Concise Description of Outstanding Issues: (R03) – None

[redacted] (b) (4)

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Summary of the Information

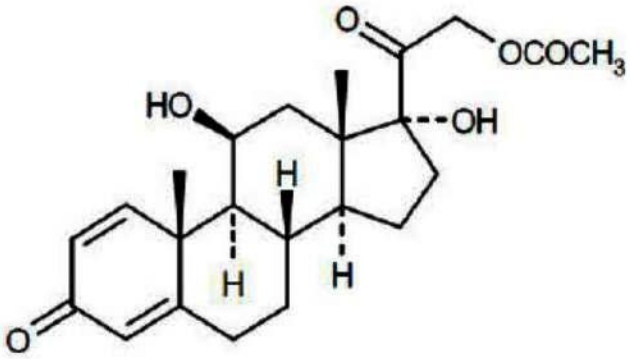
1.0 NOMENCLATURE

Recommended International Non-proprietary Name (rINN)	:	**Prednisolone Acetate**
Compendial name	:	**Prednisolone Acetate**
Chemical Name(s) (IUPAC)	:	**Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-, (11β)-.** **11β, 17-dihydroxy-3,20-dioxopregna,1,4-dien-21-yl-acetate** **11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-acetate**
Chemical Abstract Service (CAS) Registry Number	:	**[52-21-1]**

STRUCTURE

Molecular Formula : $C_{23}H_{30}O_6$

Structural Formula :



Molecular Weight : 402.48

General Properties for the Drug Substance provided in 3.2.S.1.3: Link

Attributes	Description
Description	White to practically white, odorless crystalline powder.

(b) (4)

[redacted]

Post-Approval Stability Protocol and Commitment

POST APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

Reference is incorporated of the Type II Drug Master File for Prednisolone Acetate USP [DMF No. (b) (4)

Assessment: *{Adequate}*
The applicant references DMF (b) (4) in support of post-approval stability protocol and stability commitment for the DS.

R REGIONAL INFORMATION

Comparability Protocols

Assessment: N/A
Comparability protocol is not required for this ANDA submission.

Lifecycle Management Considerations

None

DRUG SUBSTANCE LIST OF DEFICIENCIES (R03)

None

(b) (4)

[redacted]

Primary Drug Substance Assessor Name and Date: Shirshendu Deb, 8/22/2022 (R01), 11/08/2022 & 11/09/2022 (R01a), 03/18/2024 (R02), 06/17/2024, 07/16/2024 (R03).

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Yongneng (Frank) Yao, 24Aug2022, 26Aug2022.
Yili Li, 11/10/2022 (R01a); 3/19/2024 (R02); 7/16/2024 (R03)

CHAPTER II: DRUG PRODUCT

For more details about the items in this template, please see Chapter II (Drug Product) of the ANDA IQA Guide

ANDA Number	A216935
Assessment Cycle Number	R03
Drug Product (DP) Name / Strength	Prednisolone Acetate Ophthalmic Suspension USP, 1% 5 mL in 10 mL bottle 10 mL in 15 mL bottle 15 mL in 15 mL bottle
Route of Administration	Ophthalmic
Drug Product Manufacturer	Lupin Limited
RLD/RS Information (Brand Name of Product, Applicant)	Drug Brand Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL
RLD/RS Number	NDA 017011
Proposed Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

MDD = [redacted] (b) (4) of DP proposed by A216935 sponsor.

	ICH Impurity Threshold (MDD = (b) (4), proposed by A216935 sponsor, see the assessment below regarding MDD)		
	Report	**Identification**	**Qualification**
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	(b) (4) 20 µg/day	(b) (4) 50 µg/day

******Not for FOIA**********

(b) (4)

[redacted]

(b) (4)

	ICH Impurity Threshold (MDD = (b) (4) mg in RLD)		
	Report	**Identification**	**Qualification**
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	(b) (4) 20 µg/day	(b) (4) 50 µg/day

RLD's MDD (b) (4) (link)
Per RLD package insert

DOSAGE AND ADMINISTRATION

Shake well before using. Instill one to two drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased if necessary. Care should be taken not to discontinue therapy prematurely.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated (see PRECAUTIONS).

(b) (4)

1.2 Maximum Daily Dose Calculations and Assumptions

The maximum daily dose (MDD) is defined as the largest dose that is safe to administer. The density values of a variety of Allergan products range from (b) (4) For ease of evaluation, a density value of (b) (4) is used to obtain the MDD according to equation below. The maximum daily dose for PRED FORTE® is provided in Table 1.

(b) (4)

****

Assessment Recommendation: **Adequate**

If Inadequate-Major, select Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

If Inadequate-Major, enter Justification: *(Click link to view Justification Statements)*

N/A
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary:
Prednisolone acetate Ophthalmic Suspension is a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. The RLD product is PRED FORTE, 1% by Allergan, Inc. approved prior to Jan 1, 1982. The therapeutic code is "AB" meaning "actual or potential bioequivalence problems have been resolved through adequate in vivo and/or in vitro testing".

Proposed indication for use: Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
DS solid state form stability	3	4	4	48	(b) (4)
DS particle size stability	3+1+1=5	4	4	80	

(b) (4)

[redacted] (b) (4)

Assay (Active)	2	3	3	18
Assay (Antimicrobial preservative)	2+2=4	3	3	36
Assay (Antioxidant)	2	3	3	18

[redacted] (b) (4)

Chemical Stability (All CQAs)	2	3	3	18

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Sterility	3	4	3	36
Color	2	3	3+2=5	30
Bulk content uniformity (in process)	4-2=2	4	4	32

					(b) (4)
DP Phase stability (sedimentation/re-suspendability/ Drop homogeneity)	4-1-1-1= 1	4	4	16	
Drop size	2	3	3	18	

					(b) (4)
Antimicrobial effectiveness (USP<51>)	3	4	3	36	
Weight loss (Stability)	3	3	3	27	
pH	2	3	3	18	

Viscosity	2	3	3	18
Extractable/leachable	3	3	3	27

(b) (4)

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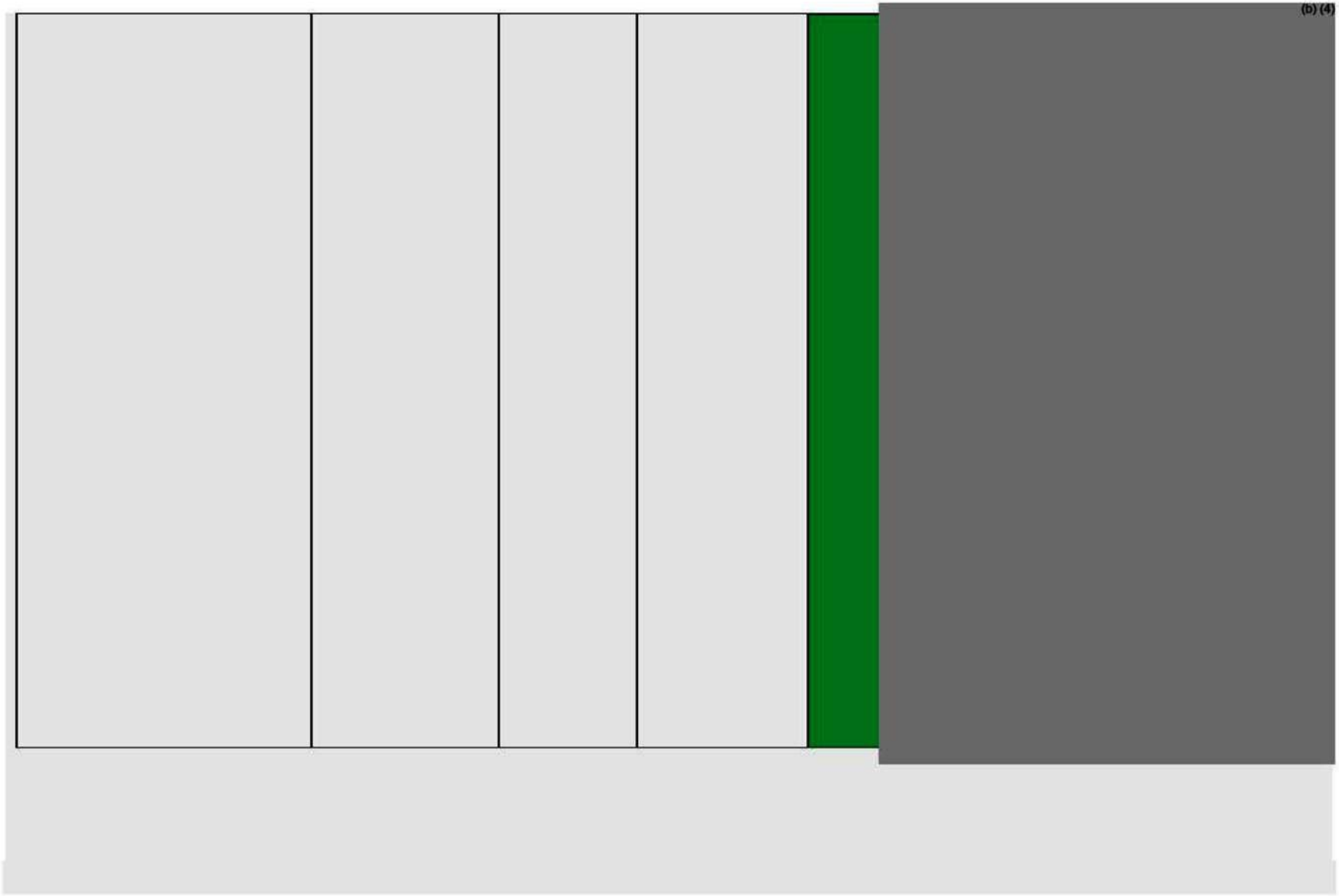
(b) (4)

Additional CQAs/Risks identified by ATL					(b) (4)


(b) (4)

Concise Description of current Outstanding Issues: (R03):

None

Highlight Key Issues from Last Cycle (R02, CRL) & Their Resolution:

(b) (4)

Resolved

(b) (4)

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(b) (4)

[redacted]

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status:* **N/A**
- *Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data meets revised specifications (if applicable) to confirm shelf life proposal* **No**
- *Elemental impurity controlled per USP<232> and <233> requirements or ICH Q3D recommendations – status:* **Yes**
- *Number of Comparability protocols included:* **0**

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Table 1: Description of the Drug Product

Fill Volume	Description
5 mL [redacted] (b) (4) 10 mL round opaque white [redacted] (b) (4) bottle)	White to off-white milky fine suspension filled in opaque white bottle closed with opaque white nozzle and then with white cap.
10 mL [redacted] (b) (4) 15 mL round opaque white [redacted] (b) (4) bottle)	
15 mL [redacted] (b) (4) 15 mL round opaque white [redacted] (b) (4) bottle)	

Table 3: Qualitative and Quantitative Composition of the Drug Product

Ingredients [Grade]	1%			Category	Reference to Standards
	Unit Quantity (mg/mL)	%w/v	%w/w		
Prednisolone acetate* $ (b) (4) micronized)	(b) (4)	1.000	1.000	Active Ingredient	USP
Benzalkonium Chloride (b) (4) (b) (4)			(b) (4)	Preservative	NF
Edetate disodium (b) (4)				(b) (4)	USP
Polysorbate 80					NF
Sodium Bisulfite#					IH
Hypromellose (b) (4) (b) (4)					USP
Boric Acid					NF
Sodium Citrate (b) (4) (b) (4)					USP
Sodium Chloride					USP
Water for Injection¥					USP
(b) (4) (b) (4)					

Note: We would like to inform the Agency that we have received agency's confirmation w.r.t. Q1 and Q2 sameness of our drug product with the reference listed drug, PRED FORTE® (prednisolone acetate ophthalmic suspension USP) 1%. Please refer the Agency's Correspondence Response (#37229) dated August 04, 2021 to our Controlled Correspondence dated June 23, 2021. We have used (b) (4) as proposed in above controlled correspondence.

Table 4: IIG Limits for the Excipients Used in the Drug Product

Ingredient [Grade]	Maximum Amount in mg per mL [unit dose]	Quantity per Dosage Unit (%w/w)/ (%w/v)	Maximum amount in mg per mL based on Maximum Daily Dose (MDD) (%)	Recommended IID Levels (%w/v) (Ophthalmic Route)	Reference to Standards
Benzalkonium Chloride (b) (4) (b) (4)				(b) (4)	NF
Edetate disodium (b) (4)					USP
Polysorbate 80					NF
Sodium Bisulfite					IH
Hypromellose USP (b) (4) (b) (4)					USP
Boric Acid					NF
Sodium Citrate (b) (4) (b) (4) USP (b) (4)					USP
Sodium Chloride					USP

IID - Inactive Ingredient Database; (b) (4)

(b) (4)

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3.2.P.3.2 Batch Formula [PRED FORTE® Ophthalmic Suspension]

(b) (4)

Table 1 Quantitative Composition for the Drug Product

Ingredients	Reference to Standards	Concentration (% w/v)	Concentration (mg/mL)
Prednisolone Acetate	USP / Ph. Eur	(b) (4)	
Benzalkonium Chloride[1]	NF / Ph. Eur		
Edetate Disodium	USP / Ph. Eur		
Boric Acid	NF / Ph. Eur		
Sodium Citrate, (b) (4)	USP / Ph. Eur		
Sodium Bisulfate	FCC		
Sodium Chloride	USP / Ph. Eur		
Polysorbate 80[2]	NF / Ph. Eur		
Hypromellose	USP / Ph. Eur		
Purified Water	USP / Ph. Eur		

(b) (4)

****

Prednisolone acetate – *(PSG Draft Guidance)*:
"Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentration as the RLD. For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulation for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."

Drug Substance:
Prednisolone acetate, USP (micronized, (b) (4) is used by the ANDA applicant.

(b) (4)

[redacted] (b) (4)

Inactive Ingredients' Quality (Q1):
The DP is Q1 same with respect to the RLD [redacted] (b) (4)

DP composition (Q2):
As per CC # 37229, the agency acknowledged (correspondence receipt date: 6/23/2021; correspondence response date: 8/4/2021) that "OGD would not likely refuse to receive an abbreviated new drug application (ANDA)" for the DP composition proposed on June 23, 2021.
"Reference is made to the definition of **quantitative sameness** to the reference listed drug (RLD) as stated in the guidance for industry on ANDA Submissions - Refuse-to-Receive Standards (December 2016, Revision 2)."
The applicant developed one of the two formulations proposed in the correspondence dated June 23, 2021.

Table: Evaluation of quantitative sameness (Q2)

Ingredients	DP formulation (% w/v)	RLD (% w/v) [not for FOIA]	Assessor comments
Prednisolone Acetate	1.00	(b) (4)	Q2 comparable
Benzalkonium Chloride	(b) (4)		Q2 comparable
Edetate Disodium			Q2 same
Boric Acid			Q2 comparable
Sodium Citrate, (b) (4)			Q2 comparable
Sodium Bisulfite			Q2 comparable
Sodium Chloride			Q2 comparable
Polysorbate 80			Q2 comparable[1]
Hypromellose			Q2 same
WFI			Q2 comparable

(b) (4)

1 Page has been withheld in full as b4 (CCI/TS) immediately

1.3.5 Composition of Reference Product Pred Forte® and Test Product

Table 1.3: The qualitative formulation details of Pred Forte® (prednisolone acetate ophthalmic suspension USP) 1 % and Test Product (prednisolone acetate ophthalmic suspension USP) 1%

Reference Product Pred Forte® (prednisolone acetate ophthalmic suspension, USP) 1 % Distributed By: Allergan USA, Inc., Madison, NJ.	Proposed Test Drug Product Prednisolone acetate ophthalmic suspension USP, 1 % Manufactured by Lupin Limited, Pithampur, India	Functional Category in the Proposed Test Drug Product
Active Ingredient	**Active Ingredient**	-
Prednisolone Acetate	Prednisolone Acetate	Active
Inactive Ingredients	**Inactive Ingredients**	-
Benzalkonium chloride	Benzalkonium chloride	Preservative
Boric acid	Boric acid	(b) (4)
Edetate disodium	Edetate disodium	
Hypromellose	Hypromellose	
Polysorbate 80	Polysorbate 80	
Sodium bisulfite	Sodium bisulfite	
Sodium chloride	Sodium chloride	
Sodium citrate	Sodium citrate	
purified water	Water for Injection	

Table 1.6: Quantitative estimation of excipients and physico-chemical characterization of Pred Forte® (prednisolone acetate ophthalmic suspension, USP) 1 %

Pred Forte® (Prednisolone acetate ophthalmic suspension USP) 1 % Lot No: 86334 and 90177		
Ingredients	**Label claim (mg/mL)**	**Results (mg/mL)** **(Average of four analysis)**
Prednisolone Acetate	(b) (4)	
Benzalkonium chloride		
Boric acid		
Edetate disodium		
Hypromellose		
Polysorbate 80		
Sodium bisulfite		
Sodium chloride		
Sodium citrate		
	(b) (4)	

NA: Not Applicable

(b) (4)

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(b) (4)

[redacted]

R REGIONAL INFORMATION

Environmental

Assessment: ***{Adequate}***
The Environmental Impact Analysis Statement is provided in Section 1.12.14, reference is made to 21 CFR 25.31(a) and 21 CFR 25.15(d) . Acceptable

Methods Validation or Verification Package

Assessment: ***{N/A}***
Refer to review of 3.2.P.5.3.

Comparability Protocols

Assessment: ***{N/A}***
No Comparability Protocols are proposed.

Lifecycle Management Considerations

N/A

DRUG PRODUCT LIST OF DEFICIENCIES (R03)

None

(b) (4)

[redacted]

Primary Drug Product Assessor Name and Date: Shirshendu Deb, 8/22/2022, 8/26/2022. 11/08/2022, 11/10/2022 (R01a, CRL), 03/18/2024 (R02), 06/17/2024, 07/16/2024 (R03).

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yongeng (Frank) Yao, 25Agu2022, 26Aug2022. Yili Li, 11/10/2022 (R01a); 3/19/2024 (R02); 7/16/2024 (R03)

CHAPTER III: ENVIRONMENTAL

For more details about the items in this template, please see Chapter III (Environmental) of the ANDA IQA Guide

R REGIONAL INFORMATION

Environmental

Assessment: ***{Adequate}***
The applicant has submitted Categorical Exclusion claim under 21 CFR 25.31(a) and a statement certifying compliance with 21 CFR 25.15(d).

Primary Environmental Assessor Name and Date: Shirshendu Deb, 8/26/2022, 11/08/2022 (R01a, CRL), 03/18/2024 (R02).

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yili Li, 3/19/2024

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the ANDA IQA Guide

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)? _____

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:

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

Assessment (R#01): in-use stability study is pending. (b) (4) .

If "No," explain.

For OTC Drugs and Controlled Substances:

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:

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None (R#01)

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

R#01: None

Primary Drug Product Assessor Name and Date: Shirshendu Deb, 8/22/2022, 8/26/2022, 11/08/2022 (R01a), 03/18/2024 (R02), 06/17/2024, 07/16/2024 (R03).

Secondary Drug Product Assessor Name and Date: Yongneng (Frank) Yao, 25Aug2022, 26Aug2022. Yili Li, 11/10/2022 (R01a); 3/19/2024 (R02).

R REGIONAL INFORMATION

Comparability Protocols

Assessment: *{N/A}*

Lifecycle Management Considerations

N/A

Shirshendu Deb

Digitally signed by Shirshendu Deb
Date: 7/16/2024 04:57:39PM
GUID: 617aac23007c0baef3c826610ebf0887

Yili Li

Digitally signed by Yili Li
Date: 7/16/2024 04:39:05PM
GUID: 57573c63003677e420bfae1fb7770d72

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	216935
Review Cycle #	02
Applicant Name	Lupin Limited
Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP
Dosage Form. (click (+) for more than one)	Suspension
Proposed Strength(s)	1%
Route of Administration (click (+) for more than one)	Ophthalmic
Maximum Daily Dose	(b) (4)
Rx/OTC Dispensed	Rx
Proposed Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Drug Product Description	Prednisolone acetate ophthalmic suspension USP, 1% is a sterile, topical anti-inflammatory agent for ophthalmic use. Each mL of prednisolone acetate ophthalmic suspension USP contains: **Active:** prednisolone acetate (micronized) 1% **Inactive:** benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection. The pH during its shelf life ranges from 5.0 to 6.0.
Co-packaged product information	None
Device information, if any:	None

Storage Temperature/ Conditions	Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Shirshendu Deb	Yili Li
	Drug Product/ Labeling	Shirshendu Deb	Yili Li
	Manufacturing	Yuesheng Ye	Aditi Thakur
	Biopharmaceutics	Parnali Chatterjee	
	Microbiology	Ryan Blower	Bethanie Lee
	Other (specify):		
	RBPM	Tristen Cook	
	ATL	Yili Li	

Consults	**Discipline Consulted**	**Recommendation**	**Date**
	None		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
New ANDA SD 2	04/11/2022	All
Response to IR SD 4	07/28/2022	Quality
Response to IR SD 5	08/26/2022	Quality
Response to DRL SD 9	10/07/2022	Quality
Resubmission SD 10	10/17/2023	DP, Manufacturing
Response to IR SD 11	01/05/2024	BioPharm

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Prednisolone Acetate, USP	IQ	03/11/2024	Per DMF Chemistry R#02, Yongjun Gao
	III		(b) (4)	N/A		Referenced in multiple approved ANDA and/or NDA including suspension (A064065)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N203491)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N021373)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A064135)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A210765)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N019845)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A065307)
	III					Referenced in multiple approved ANDA and/or NDA (A206716-powder, for solution)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A212450)

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N017011	Drug Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL Approval Date: Approved Prior to Jan 1, 1982
ANDA	N/A	No approved ANDA for prednisolone acetate ophthalmic suspension is currently active.

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Drug Substance: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Drug Product: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Manufacturing: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Biopharmaceutics: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Comments:

ANDA 216935
Assessment R02

Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP
Dosage Form	Suspension
Strength	1%
Route of Administration	Ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Lupin Limited
US agent, if applicable	Ms. Kalpana Vanam [Senior Vice President, Regulatory Affairs] Lupin Pharmaceuticals, Inc., 400 Campus Drive, Somerset, NJ 08873 (b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001	01-21-2022	All
0002	04-11-2022	All
0004	07-28-2022	Quality
0005	08-26-2022	Quality (3.2.P.3)
0009 (R01a)	10-07-2022	Quality (both DS & DP sections)
0010 (R02)	10-17-2023	Quality
0011 (R02)	01-05-2024	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance*		
Drug Product	Shirshendu Deb	Yongneng Yao (DRL), Yili Li
Manufacturing		
Microbiology		
Biopharmaceutics		
Regulatory Business Process Manager		
Application Technical Lead		
Laboratory (OTR)		
Environmental		

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Prednisolone Acetate, USP	IQ	03/11/2024	Per DMF Chemistry R#02, Yongjun Gao
	III		(b) (4)	N/A		Referenced in multiple approved ANDA and/or NDA including suspension (A064065)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N203491)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N021373)
	III					Referenced in multiple approved ANDA and/or NDA

(b) (4)		(b) (4)			
					including suspension (A064135)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (A210765)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (N019845)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (A065307)
	III				Referenced in multiple approved ANDA and/or NDA (A206716-powder, for solution)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (A212450)

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N017011	Drug Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL Approval Date: Approved Prior to Jan 1, 1982
ANDA	N/A	No approved ANDA for prednisolone acetate ophthalmic suspension is currently active.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Proposed limits of NMT (b) (4) % are acceptable for each of the impurities: (b) (4)	3/18/2024	Vincent Crowley
CDRH				
Clinical				
Other				

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CHAPTER I: DRUG SUBSTANCE

For more details about the items in this template, please see Chapter I (Drug Substance) of the ANDA IQA Guide

Drug Substance Name	Prednisolone Acetate
ANDA Number	A216935
Applicant Name	Lupin Limited
Assessment Cycle Number	R02
DMF Number (if applicable)	(b) (4)
DMF Status	**Inadequate-Minor**
DMF Holder	(b) (4)

Assessment Recommendation: **Inadequate-Minor**

If Inadequate-Major, select Theme:

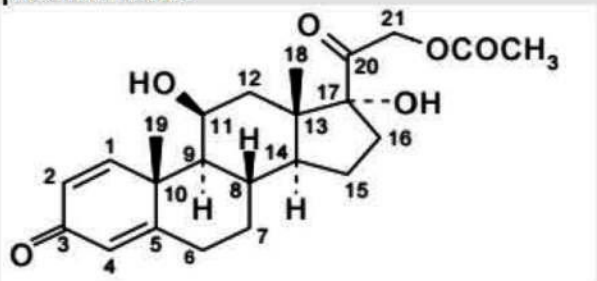
☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

If Inadequate-Major, enter Justification: *(Click link to view Justification Statements)*

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Prednisolone acetate is a compendial drug substance (CAS: 52-21-1) used to treat eye conditions due to inflammation or injury. The DS belongs to a synthetic glucocorticoid corticosteroid. It is the 21-acetate ester of prednisolone.



Therapeutic category: Indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

The molecular formula is $C_{23}H_{30}O_6$ and the molecular weight is 402.49 g/mol. The DS has poor water solubility but is soluble in organic solvents like chloroform, methanol, and ethanol. (b) (4)

(b) (4)

The firm referred to DMF (b) (4) for information regarding the chemistry, manufacturing and controls used in the production of Prednisolone acetate, micronized. The DMF review is IQ-Minor (Reviewer Yongjun Gao)

(b) (4)

S.1 GENERAL INFORMATION

Summary of the Information

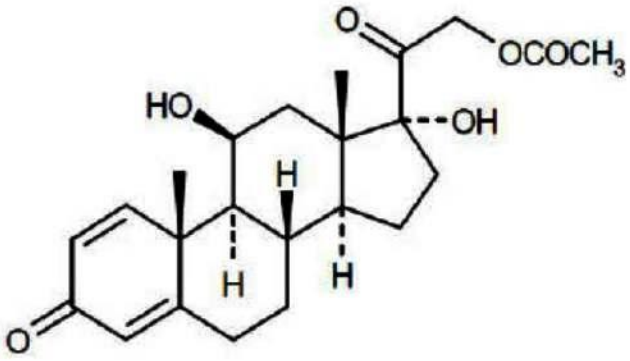
1.0 NOMENCLATURE

Recommended International Non-proprietary Name (rINN)	:	**Prednisolone Acetate**
Compendial name	:	**Prednisolone Acetate**
Chemical Name(s) (IUPAC)	:	**Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-, (11β)-.** **11β, 17-dihydroxy-3,20-dioxopregna,1,4-dien-21-yl-acetate** **11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-acetate**
Chemical Abstract Service (CAS) Registry Number	:	**[52-21-1]**

STRUCTURE

Molecular Formula : $C_{23}H_{30}O_6$

Structural Formula :



Molecular Weight : 402.48

General Properties for the Drug Substance provided in 3.2.S.1.3: Link

Attributes	Description
Description	White to practically white, odorless crystalline powder.
Solubility	Slightly soluble in acetone, in alcohol and in chloroform. Practically insoluble in water.

(b) (4)

Post-Approval Stability Protocol and Commitment

POST APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

Reference is incorporated of the Type II Drug Master File for Prednisolone Acetate USP [DMF No. (b) (4)

Assessment: *{Adequate}*
The applicant references DMF (b) (4) in support of post-approval stability protocol and stability commitment for the DS.

R REGIONAL INFORMATION

Comparability Protocols

Assessment: N/A
Comparability protocol is not required for this ANDA submission.

Lifecycle Management Considerations

None

DRUG SUBSTANCE LIST OF DEFICIENCIES (R02)

(b) (4)

(b) (4)

Primary Drug Substance Assessor Name and Date: Shirshendu Deb, 8/22/2022 (R01), 11/08/2022 & 11/09/2022 (R01a), 03/18/2024 (R02)

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Yongneng (Frank) Yao, 24Aug2022, 26Aug2022.
Yili Li, 11/10/2022 (R01a); 3/19/2024 (R02).

CHAPTER II: DRUG PRODUCT

For more details about the items in this template, please see Chapter II (Drug Product) of the ANDA IQA Guide

ANDA Number	A216935
Assessment Cycle Number	R02
Drug Product (DP) Name / Strength	Prednisolone Acetate Ophthalmic Suspension USP, 1% 5 mL in 10 mL bottle 10 mL in 15 mL bottle 15 mL in 15 mL bottle
Route of Administration	Ophthalmic
Drug Product Manufacturer	Lupin Limited
RLD/RS Information (Brand Name of Product, Applicant)	Drug Brand Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL
RLD/RS Number	NDA 017011
Proposed Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

MDD = [redacted] (b) (4) of DP proposed by A216935 sponsor.

	ICH Impurity Threshold (MDD = (b) (4), proposed by A216935 sponsor, see the assessment below regarding MDD)		
	Report	**Identification**	**Qualification**
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	(b) (4) 20 µg/day	(b) (4) 50 µg/day

******Not for FOIA**********

(b) (4)

[redacted]

(b) (4)

[redacted]

	ICH Impurity Threshold (MDD = (b) (4) in RLD)		
	Report	**Identification**	**Qualification**
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	(b) (4) 20 µg/day	(b) (4) 50 µg/day

RLD's MDD (b) (4) (link)

Per RLD package insert

DOSAGE AND ADMINISTRATION

Shake well before using. Instill one to two drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased if necessary. Care should be taken not to discontinue therapy prematurely.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated (see PRECAUTIONS).

(b) (4)

[redacted]

1.2 Maximum Daily Dose Calculations and Assumptions

The maximum daily dose (MDD) is defined as the largest dose that is safe to administer. The density values of a variety of Allergan products range from (b) (4) For ease of evaluation, a density value of (b) (4) is used to obtain the MDD according to equation below. The maximum daily dose for PRED FORTE® is provided in Table 1.

(b) (4)

[redacted]

Assessment Recommendation: **Inadequate-Minor**

If Inadequate-Major, select Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

If Inadequate-Major, enter Justification: *(Click link to view Justification Statements)*

N/A
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary:
Prednisolone acetate Ophthalmic Suspension is a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. The RLD product is PRED FORTE, 1% by Allergan, Inc. approved prior to Jan 1, 1982. The therapeutic code is "AB" meaning "actual or potential bioequivalence problems have been resolved through adequate in vivo and/or in vitro testing".

Proposed indication for use: Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
DS solid state form stability	3	4	4	48	(b) (4) [redacted]
DS particle size stability	3+1+1=5	4	4	80	

(b) (4) [redacted]

[redacted] (b) (4)

Assay (Active)	2	3	3	18
Assay (Antimicrobial preservative)	2+2=4	3	3	36
Assay (Antioxidant)	2	3	3	18
Chemical Stability (All CQAs)	2	3	3	18

[redacted] (b) (4)

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[redacted] (b) (4)

Sterility	3	4	3	36
Color	2	3	3+2=5	30
Bulk content uniformity (in process)	4-2=2	4	4	32
DP Phase stability (sedimentation/re-suspendability/	4-1-1-1= 1	4	4	16

[redacted] (b) (4)

Drop homogeneity)					(b) (4)
Drop size	2	3	3	18	
Antimicrobial effectiveness (USP<51>)	3	4	3	36	

					(b) (4)
Weight loss (Stability)	3	3	3	27	
pH	2	3	3	18	
Viscosity	2	3	3	18	

					(b) (4)
Extractable/leachable	3	3	3	27	

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(b) (4)

[redacted]

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status:* **N/A**
- *Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data meets revised specifications (if applicable) to confirm shelf life proposal* **No**
- *Elemental impurity controlled per USP<232> and <233> requirements or ICH Q3D recommendations – status:* **Yes**
- *Number of Comparability protocols included:* **0**

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Table 1: Description of the Drug Product

Fill Volume	Description
5 mL [redacted] (b) (4) 10 mL round opaque white [redacted] (b) (4) bottle)	White to off-white milky fine suspension filled in opaque white bottle closed with opaque white nozzle and then with white cap.
10 mL [redacted] (b) (4) 15 mL round opaque white [redacted] (b) (4) bottle)	
15 mL [redacted] (b) (4) 15 mL round opaque white [redacted] (b) (4) bottle)	

Table 3: Qualitative and Quantitative Composition of the Drug Product

Ingredients [Grade]	1%			Category	Reference to Standards
	Unit Quantity (mg/mL)	%w/v	%w/w		
Prednisolone acetate* $ (b) (4) micronized)	(b) (4)	1.000	1.000	Active Ingredient	USP
Benzalkonium Chloride (b) (4) (b) (4)			(b) (4)	Preservative	NF
Edetate disodium (b) (4)				(b) (4)	USP
Polysorbate 80					NF
Sodium Bisulfite#					IH
Hypromellose (b) (4) (b) (4)					USP
Boric Acid					NF
Sodium Citrate (b) (4) (b) (4)					USP
Sodium Chloride					USP
Water for Injection¥					USP
(b) (4)					
(b) (4)					

Note: We would like to inform the Agency that we have received agency's confirmation w.r.t. Q1 and Q2 sameness of our drug product with the reference listed drug, PRED FORTE® (prednisolone acetate ophthalmic suspension USP) 1%. Please refer the Agency's Correspondence Response (#37229) dated August 04, 2021 to our Controlled Correspondence dated June 23, 2021. We have used (b) (4) as proposed in above controlled correspondence.

Table 4: IIG Limits for the Excipients Used in the Drug Product

Ingredient [Grade]	Maximum Amount in mg per mL [unit dose]	Quantity per Dosage Unit (%w/w)/ (%w/v)	Maximum amount in mg per mL based on Maximum Daily Dose (MDD) (%)	Recommended IID Levels (%w/v) (Ophthalmic Route)	Reference to Standards
Benzalkonium Chloride (b) (4) (b) (4)					NF
Edetate disodium (b) (4)					USP
Polysorbate 80					NF
Sodium Bisulfite					IH
Hypromellose USP (b) (4) (b) (4)					USP
Boric Acid					NF
Sodium Citrate (b) (4) (b) (4) USP (b) (4)					USP
Sodium Chloride					USP

IID - Inactive Ingredient Database: (b) (4)

(b) (4)

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3.2.P.3.2 Batch Formula [PRED FORTE® Ophthalmic Suspension]

(b) (4)

[redacted]

Table 1 Quantitative Composition for the Drug Product

Ingredients	Reference to Standards	Concentration (% w/v)	Concentration (mg/mL)
Prednisolone Acetate	USP / Ph. Eur	(b) (4) [redacted]	
Benzalkonium Chloride(1)	NF / Ph. Eur		
Edetate Disodium	USP / Ph. Eur		
Boric Acid	NF / Ph. Eur		
Sodium Citrate, (b) (4) [redacted]	USP / Ph. Eur		
Sodium Bisulfate	FCC		
Sodium Chloride	USP / Ph. Eur		
Polysorbate 80(2)	NF / Ph. Eur		
Hypromellose	USP / Ph. Eur		
Purified Water	USP / Ph. Eur		

(b) (4) [redacted]

****

Prednisolone acetate – *(PSG Draft Guidance)*:
"Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentration as the RLD. For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulation for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."

Drug Substance:
Prednisolone acetate, USP (micronized, (b) (4) [redacted] is used by the ANDA applicant.

(b) (4) [redacted]

(b) (4)

Inactive Ingredients' Quality (Q1):
The DP is Q1 same with respect to the RLD (b) (4)

DP composition (Q2):
As per CC # 37229, the agency acknowledged (correspondence receipt date: 6/23/2021; correspondence response date: 8/4/2021) that "OGD would not likely refuse to receive an abbreviated new drug application (ANDA)" for the DP composition proposed on June 23, 2021.
"Reference is made to the definition of **quantitative sameness** to the reference listed drug (RLD) as stated in the guidance for industry on ANDA Submissions - Refuse-to-Receive Standards (December 2016, Revision 2)."
The applicant developed one of the two formulations proposed in the correspondence dated June 23, 2021.

Table: Evaluation of quantitative sameness (Q2)

Ingredients	DP formulation (% w/v)	RLD (% w/v) [not for FOIA]	Assessor comments
Prednisolone Acetate	1.00	(b) (4)	Q2 comparable
Benzalkonium Chloride	(b) (4		Q2 comparable
Edetate Disodium			Q2 same
Boric Acid			Q2 comparable
Sodium Citrate, (b) (4)			Q2 comparable
Sodium Bisulfite			Q2 comparable
Sodium Chloride			Q2 comparable
Polysorbate 80			Q2 comparable[1]
Hypromellose			Q2 same
WFI			Q2 comparable

(b) (4)

CHAPTER III: ENVIRONMENTAL

For more details about the items in this template, please see Chapter III (Environmental) of the ANDA IQA Guide

R REGIONAL INFORMATION

Environmental

Assessment: ***{Adequate}***
The applicant has submitted Categorical Exclusion claim under 21 CFR 25.31(a) and a statement certifying compliance with 21 CFR 25.15(d).

Primary Environmental Assessor Name and Date: Shirshendu Deb, 8/26/2022, 11/08/2022 (R01a, CRL), 03/18/2024 (R02).

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yili Li, 3/19/2024

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the ANDA IQA Guide

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)? _____

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:

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

Assessment (R#01): in-use stability study is pending. (b) (4)

If "No," explain.

For OTC Drugs and Controlled Substances:

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:

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None (R#01)

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

R#01: None

Primary Drug Product Assessor Name and Date: Shirshendu Deb, 8/22/2022, 8/26/2022, 11/08/2022 (R01a), 03/18/2024 (R02).

Secondary Drug Product Assessor Name and Date: Yongneng (Frank) Yao, 25Aug2022, 26Aug2022. Yili Li, 11/10/2022 (R01a); 3/19/2024 (R02).

R REGIONAL INFORMATION

Comparability Protocols

Assessment: *{N/A}*

Lifecycle Management Considerations

N/A

Shirshendu Deb

Digitally signed by Shirshendu Deb
Date: 3/19/2024 09:33:33AM
GUID: 617aac23007c0baef3c826610ebf0887

Yili Li

Digitally signed by Yili Li
Date: 3/19/2024 09:30:36AM
GUID: 57573c63003677e420bfae1fb7770d72

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA-216935-ORIG-1-AMEND-10
Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP (5mL, 10mL, 15mL)
Strengths	1%
Dosage Form	Suspension
Administration Route	Ophthalmic
Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Applicant Name	Lupin Limited
RLD Number	N017011
Primary Assessor	
Secondary Assessor	

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Inadequate - Minor

Assessment Summary:

Facilities: Withhold is recommended due to unacceptable OAI compliance status of both the DS and DP manufacturing sites due to GMP inspections results.

Pre-approval inspection of the Lupin (FEI: 3007549629) (b) (4) manufacturing facility is also needed once the compliance status is resolved. The facility does not have a history of manufacturing suspensions. The other facilities (lab testing sites) proposed are acceptable.

Process: Withhold is recommended. The risks of the proposed manufacturing operations are not fully mitigated by the development data, exhibit batch data, and process controls. (b) (4)

Product Description:

1.0 DESCRIPTION OF DOSAGE FORM

Table 1: Description of the Drug Product

Fill Volume	Description
5 mL [redacted] 10 mL round opaque white [redacted] bottle)	White to off-white milky fine suspension filled in opaque white bottle closed with opaque white nozzle and then with white cap.
10 mL [redacted] 15 mL round opaque white [redacted] bottle)	
15 mL [redacted] 15 mL round opaque white [redacted] bottle)	

Dosage:

DOSAGE AND ADMINISTRATION

Shake well before using. Instill one to two drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased if necessary. Care should be taken not to discontinue therapy prematurely.

[redacted]

Process Description:

[redacted]

3.0 INTENDED COMMERCIAL BATCH MANUFACTURING RECORDS AND PACKAGING RECORDS

[redacted]

Product	Fill Volume	Exhibit Batch Size	Intended Commercial Batch Size	Scale Up
Prednisolone Acetate Ophthalmic Suspension USP 1%	5 mL in 10 mL [redacted] Bottle	[redacted]		
	10 mL in 15 mL [redacted] Bottle			
	15 mL in 15 mL [redacted] Bottle			

Following intended commercial batch production records are provided under in this section.

Amendment review (ANDA-216935-ORIG-1-AMEND-10):
The previous review project was ANDA-216935-ORIG-1. This review is under the project, ANDA-216935-ORIG-1-AMEND-10, the 3rd round review in the 2nd review cycle.

Process: The process was inadequate (b) (4) [redacted] The process remains inadequate minor.

Facility: (b) (4) [redacted] Facility is recommended for approval for this review cycle with PoAI consideration for the DP manufacturing facility.

Note:
(b) (4) [redacted]. Not addressed in this review.

All the updates made in the following IQA are indicated with Calibri font.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
PFC (SD 1)	01/21/2022
Original Submission (SD 2)	04/11/2022
Request for SEPT 14, 2022, Mid-Cycle Meeting (SD 3)	06/08/2022
Response to Micro IR (SD 5)	08/26/2022
Response to Quality IR (SD 9)	10/07/2022
Quality information (SD #0010)	10/17/2023
Quality information (SD #0011)	01/05/2024

Additional Submissions:

Document Description (SD #)	Date Received
Response to Biopharm IR (SD 4)	07/28/2022
Response to Clinical IR (SD 6)	09/01/2022
Response to Labeling IR (SD 7)	09/02/2022
Response to Bioequivalence (SD 8)	09/19/2022

Highlight Key Issues from Last Cycle and Their Resolution:

- The applicant does not account for [redacted] (b) (4)
- [redacted] (b) (4) Additional process development data may be required.
- Surveillance inspections found [redacted] (b) (4) and the [redacted] (b) (4), Lupin Limited (FEI: 3007549629), manufacturing facilities to be unacceptable.

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

List Number of Comparability Protocols:

1. Lifecycle Management Considerations

Post-approval inspection?	Yes. #PoAI. Facility Name/FEI:
Lifecycle considerations	Choose an item.
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
[redacted] (b) (4)			Withhold - Based on CGMP → Approve - Based on Previous History
[redacted]			Approve - Based on Previous History
M/s. Lupin Limited (Drug Product Manufacturing Site) Unit-2, Plot No. M-2 and M-2-A, Special Economic Zone, Phase - II, Misc. Zone Apparel Park, Dist- Dhar, , Pithampur,	3007549629	[redacted] (b) (4)	Withhold - Based on CGMP Pre-approval inspection of the Lupin (FEI:

Madhya Pradesh, India, 454775		(b) (4)	3007549629) drug product manufacturing facility is also needed once the compliance status is resolved. → Approve - Based on Previous History Note: PAI has not been requested in the 2nd review cycle although the compliance status has been changed to acceptable. See discussion below for details.
M/s. Lupin Limited Unit-3, Plot No. M-1 and M-3-A, Special Economic Zone, Phase – II, Misc. Zone Apparel Park,, Pithampur, Madhya Pradesh, India, 454775	3009107538		Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History

II. Drug Product Manufacturing

(b) (4)

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(b) (4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Andrew Idzior	Sateesh Sathigari	9/5/2022	IR	Withheld
2	Andrew Idzior	Sateesh Sathigari	11/7/2022	CR Minor	Withheld
3	Yuesheng Ye	N. Chidambaram, Ph.D.	3/15/2024	CR Minor	Approve

Nallaperumal Chidambaram

Digitally signed by Nallaperumal Chidambaram
Date: 3/18/2024 03:14:29PM
GUID: 505c640c00001174c4c79937c74b1367

Yuesheng Ye

Digitally signed by Yuesheng Ye
Date: 3/18/2024 03:08:54PM
GUID: 5203e2c70001f9a26cd12224ab5f697d

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	216935
Review Cycle #	01
Applicant Name	Lupin Limited
Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP
Dosage Form. (click (+) for more than one)	Suspension
Proposed Strength(s)	1%
Route of Administration (click (+) for more than one)	Ophthalmic
Maximum Daily Dose	(b) (4)
Rx/OTC Dispensed	Rx
Proposed Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Drug Product Description	Prednisolone acetate ophthalmic suspension USP, 1% is a sterile, topical anti-inflammatory agent for ophthalmic use. Each mL of prednisolone acetate ophthalmic suspension USP contains: **Active:** prednisolone acetate (micronized) 1% **Inactive:** benzalkonium chloride as preservative, boric acid, edetate disodium, hypromellose, polysorbate 80, sodium bisulfite, sodium chloride, sodium citrate and water for injection. The pH during its shelf life ranges from 5.0 to 6.0.
Co-packaged product information	None
Device information, if any:	None

Storage Temperature/ Conditions	Store at up to 25°C (77°F). Protect from freezing. Store in an upright position.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Shirshendu Deb	Yili Li
	Drug Product/ Labeling	Shirshendu Deb	Yili Li
	Manufacturing	Andrew Idzior	Sateesh Sathigari
	Biopharmaceutics	Min Sung Suh	Om Anand
	Microbiology	Ryan Blower	Bethanie Lee
	Other (specify):		
	RBPM	Christina Pleas	
	ATL	Yili Li	

Consults	**Discipline Consulted**	**Recommendation**	**Date**
	None		

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
SD1 Pre-submission	01/21/2022	All
SD2 Orig submission	04/11/2022	All
SD4 IR response	07/28/2022	Quality
SD5 IR response	08/26/2022	Quality
SD9 DRL response	10/07/2022	Quality

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Prednisolone Acetate, USP	IQ	08/17/2022	Per DMF Chemistry R#01, Yongjun Gao
	III		(b) (4)	N/A		Referenced in multiple approved ANDA and/or NDA including suspension (A064065)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N203491)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N021373)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A064135)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A210765)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N019845)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (A065307)
	III					Referenced in multiple approved ANDA and/or NDA

(b) (4)		(b) (4)			(A206716-powder, for solution)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (A212450)

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N017011	Drug Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL Approval Date: Approved Prior to Jan 1, 1982
ANDA	N/A	No approved ANDA for prednisolone acetate ophthalmic suspension is currently active.

4. Final Overall recommendation – Complete Response-Major

<u>Deficiencies</u> (if applicable):

Overall Quality Deficiencies - Optional *(Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.)*

1. None

i.

Drug Substance Deficiencies

(1 (b) (4)

Drug Product Deficiencies

(1) (b) (4)

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a. Summary of Rationale for Recommendation:

The ANDA is recommended for Inadequate-Major due to major deficiencies identified in the DP and facility.

b. Recommendation by Subdiscipline:

Drug Substance: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Drug Product: INADEQUATE-MAJOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1. The drug product deficiencies have been classified as MAJOR because new toxicology studies are requested for the unqualified impurity as noted in Appendix A, Section A(2)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of these studies require, in FDA's judgement, a substantial expenditure of FDA resources.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Manufacturing: INADEQUATE-MAJOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1. THEME: Inadequate Facility - cGMP Withhold JUSTIFICATION: The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

Biopharmaceutics: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

1.

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Comments:

ANDA 216935
Assessment R01a

Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP
Dosage Form	Suspension
Strength	1%
Route of Administration	Ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Lupin Limited
US agent, if applicable	Ms. Kalpana Vanam [Senior Vice President, Regulatory Affairs] Lupin Pharmaceuticals, Inc., 400 Campus Drive, Somerset, NJ 08873 US Agent DUNS: (b) (4)

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001	01-21-2022	All
0002	04-11-2022	All
0004	07-28-2022	Quality
0005	08-26-2022	Quality (3.2.P.3)
0009 (R01a)	10-07-2022	Quality (both DS & DP sections)

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance*		
Drug Product	Shirshendu Deb	Yongneng Yao (DRL), Yili Li
Manufacturing		
Microbiology		
Biopharmaceutics		
Regulatory Business Process Manager		
Application Technical Lead		
Laboratory (OTR)		
Environmental		

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Prednisolone Acetate, USP (b) (4)	IQ	08/17/2022	Per DMF Chemistry R#01, Yongjun Gao
	III			N/A		Referenced in multiple approved ANDA and/or NDA including suspension (A064065)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N203491)
	III					Referenced in multiple approved ANDA and/or NDA including suspension (N021373)
	III					Referenced in multiple approved ANDA and/or NDA

(b) (4)		(b) (4)			
					including suspension (A064135)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (A210765)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (N019845)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (A065307)
	III				Referenced in multiple approved ANDA and/or NDA (A206716-powder, for solution)
	III				Referenced in multiple approved ANDA and/or NDA including suspension (A212450)

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N017011	Drug Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL Approval Date: Approved Prior to Jan 1, 1982
ANDA	N/A	No approved ANDA for prednisolone acetate ophthalmic suspension is currently active.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

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CHAPTER I: DRUG SUBSTANCE

For more details about the items in this template, please see Chapter I (Drug Substance) of the ANDA IQA Guide

Drug Substance Name	Prednisolone Acetate
ANDA Number	A216935
Applicant Name	Lupin Limited
Assessment Cycle Number	R01a
DMF Number (if applicable)	(b) (4)
DMF Status	**Inadequate-Minor**
DMF Holder	(b) (4)

Assessment Recommendation: **Inadequate-Minor**

If Inadequate-Major, select Theme:

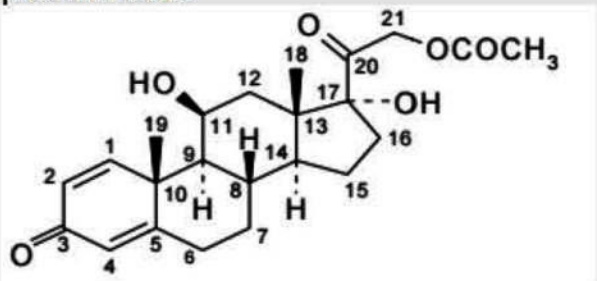
☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

If Inadequate-Major, enter Justification: *(Click link to view Justification Statements)*

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Prednisolone acetate is a compendial drug substance (CAS: 52-21-1) used to treat eye conditions due to inflammation or injury. The DS belongs to a synthetic glucocorticoid corticosteroid. It is the 21-acetate ester of prednisolone.



Therapeutic category: Indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

The molecular formula is $C_{23}H_{30}O_6$ and the molecular weight is 402.49 g/mol. The DS has poor water solubility but is soluble in organic solvents like chloroform, methanol, and ethanol. (b) (4)

(b) (4)

The firm referred to DMF (b) (4) for information regarding the chemistry, manufacturing and controls used in the production of Prednisolone acetate, micronized. The DMF review is IQ-Minor (Reviewer Yongjun Gao)

(b) (4)

S.1 GENERAL INFORMATION

Summary of the Information

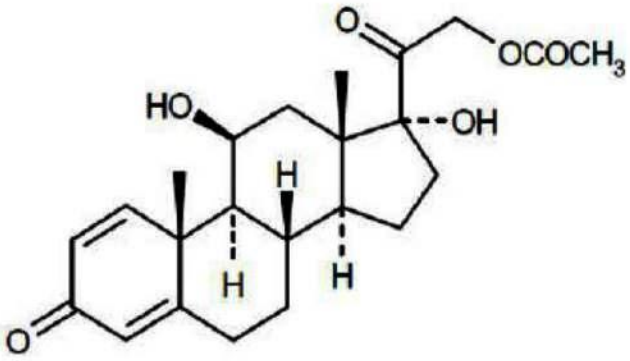
1.0 NOMENCLATURE

Recommended International Non-proprietary Name (rINN)	:	**Prednisolone Acetate**
Compendial name	:	**Prednisolone Acetate**
Chemical Name(s) (IUPAC)	:	**Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-, (11β)-.** **11β, 17-dihydroxy-3,20-dioxopregna,1,4-dien-21-yl-acetate** **11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-acetate**
Chemical Abstract Service (CAS) Registry Number	:	[52-21-1]

STRUCTURE

Molecular Formula : $C_{23}H_{30}O_6$

Structural Formula :



Molecular Weight : 402.48

General Properties for the Drug Substance provided in 3.2.S.1.3: Link

Attributes	Description
Description	White to practically white, odorless crystalline powder.
Solubility	Slightly soluble in acetone, in alcohol and in chloroform. Practically insoluble in water.

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(b) (4)

Post-Approval Stability Protocol and Commitment

POST APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

Reference is incorporated of the Type II Drug Master File for Prednisolone Acetate USP [DMF No. (b) (4)

Assessment: *{Adequate}*
The applicant references DMF (b) (4) in support of post-approval stability protocol and stability commitment for the DS.

R REGIONAL INFORMATION

Comparability Protocols

Assessment: N/A
Comparability protocol is not required for this ANDA submission.

Lifecycle Management Considerations

None

DRUG SUBSTANCE LIST OF DEFICIENCIES (R01a, CRL)

(b) (4)

(b) (4)

Primary Drug Substance Assessor Name and Date: Shirshendu Deb, 8/22/2022 (R01), 11/08/2022 & 11/09/2022 (R01a)

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Yongneng (Frank) Yao, 24Aug2022, 26Aug2022.
Yili Li, 11/10/2022

CHAPTER II: DRUG PRODUCT

For more details about the items in this template, please see Chapter II (Drug Product) of the ANDA IQA Guide

ANDA Number	A216935
Assessment Cycle Number	R01a
Drug Product (DP) Name / Strength	Prednisolone Acetate Ophthalmic Suspension USP, 1% 5 mL in 10 mL bottle 10 mL in 15 mL bottle 15 mL in 15 mL bottle
Route of Administration	Ophthalmic
Drug Product Manufacturer	Lupin Limited
RLD/RS Information (Brand Name of Product, Applicant)	Drug Brand Name: PRED FORTE, Holder: ALLERGAN PHARMACEUTICAL
RLD/RS Number	NDA 017011
Proposed Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

MDD = [redacted] (b) (4) proposed by A216935 sponsor.

	ICH Impurity Threshold (MDD = [redacted] (b) (4) proposed by A216935 sponsor, see the assessment below regarding MDD)		
	Report	**Identification**	**Qualification**
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	[redacted] (b) (4) 20 µg/day	[redacted] (b) (4) 50 µg/day

******Not for FOIA**********

MDD:

[redacted] (b) (4)

(b) (4)

[redacted]

	ICH Impurity Threshold (MDD = 7.472 mg in RLD)		
	Report	**Identification**	**Qualification**
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	[redacted] 20 µg/day	[redacted] 50 µg/day

RLD's MDD [redacted] (link)

Per RLD package insert

DOSAGE AND ADMINISTRATION

Shake well before using. Instill one to two drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased if necessary. Care should be taken not to discontinue therapy prematurely.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated (see PRECAUTIONS).

[redacted]

1.2 Maximum Daily Dose Calculations and Assumptions

The maximum daily dose (MDD) is defined as the largest dose that is safe to administer. The density values of a variety of Allergan products range from [redacted] For ease of evaluation, a density value of [redacted] is used to obtain the MDD according to equation below. The maximum daily dose for PRED FORTE® is provided in Table 1.

[redacted]

****

Assessment Recommendation: **Inadequate-Major**

If Inadequate-Major, select Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☒ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

If Inadequate-Major, enter Justification: *(Click link to view Justification Statements)*

The drug product deficiencies have been classified as MAJOR because new toxicology studies are requested for the unqualified impurity as noted in Appendix A, Section A(2)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of these studies require, in FDA's judgement, a substantial expenditure of FDA resources
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary:
Prednisolone acetate Ophthalmic Suspension is a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. The RLD product is PRED FORTE, 1% by Allergan, Inc. approved prior to Jan 1, 1982. The therapeutic code is "AB" meaning "actual or potential bioequivalence problems have been resolved through adequate in vivo and/or in vitro testing".

Proposed indication for use: Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

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(b) (4)

[redacted]

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status:* **N/A**
- *Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data meets revised specifications (if applicable) to confirm shelf life proposal* **No**
- *Elemental impurity controlled per USP<232> and <233> requirements or ICH Q3D recommendations – status:* **Yes**
- *Number of Comparability protocols included:* **0**

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
DS solid state form stability	3	4	4	48	(b) (4) [redacted]
DS particle size stability	3+1+1=5	4	4	80	

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
(b) (4)					(b) (4)
Assay (Active)	2	3	3	18	
Assay (Antimicrobial preservative)	2+2=4	3	3	36	
Assay (Antioxidant)	2	3	3	18	

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
					(b) (4)
Chemical Stability (All CQAs)	2	3	3	18	
				(b) (4)	

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
[redacted] (b) (4)					(b) (4)
Sterility	3	4	3	36	
Color	2	3	3+2=5	30	
Bulk content uniformity (in process)	4-2=2	4	4	32	
DP Phase stability (sedimentation/re-suspendability/ Drop homogeneity)	4-1-1-1= 1	4	4	16	

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
					(b) (4)
Drop size	2	3	3	18	

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
					(b) (4)
Antimicrobial effectiveness (USP<51>)	3	4	3	36	
Weight loss (Stability)	3	3	3	27	
pH	2	3	3	18	
Viscosity	2	3	3	18	

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
					(b) (4)
Extractable/leachable	3	3	3	27	

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PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
[redacted] (b) (4)					
Additional CQAs/Risks identified by ATL					(b) (4)

PRODUCT PROPERTY/CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	Comments
					(b) (4)

Risk ranking criteria:

- Product properties or CQAs that fall under a RPN of 25 are considered as **low** risk.
- Product properties or CQAs at or above RPN 25 but below 60 are considered as **moderate** risk.
- Product properties or CQAs at or above an RPN 60 are considered as **high** risk.

General Comment: For drug product, the ***Severity*** definition considered both the impact on patient safety and product quality (efficacy) failure.

Note for risk assessor and reviewer: Ophthalmic products are required to be the same (Q1/Q2) as the RLD product, including preservatives, antioxidants, buffers, tonicity agents, and thickening agent (no exception excipients are permitted). Additionally, the test product's physicochemical properties (pH, specific gravity, osmolality, and viscosity) should be comparable with those of the RLD.

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Table 1: Description of the Drug Product

Fill Volume	Description
5 mL (b) (4) 10 mL round opaque white (b) (4) bottle)	White to off-white milky fine suspension filled in opaque white bottle closed with opaque white nozzle and then with white cap.
10 mL (b) (4) 15 mL round opaque white (b) (4) bottle)	
15 mL (b) (4) 15 mL round opaque white (b) (4) bottle)	

Table 3: Qualitative and Quantitative Composition of the Drug Product

Ingredients [Grade]	1%			Category	Reference to Standards
	Unit Quantity (mg/mL)	%w/v	%w/w		
Prednisolone acetate* $ (b) (4) micronized)	(b) (4)	1.000	1.000	Active Ingredient	USP
Benzalkonium Chloride (b) (4) (b) (4)			(b) (4)	Preservative	NF
Edetate disodium (b) (4)				(b) (4)	USP
Polysorbate 80					NF
Sodium Bisulfite#					IH
Hypromellose (b) (4) (b) (4)					USP
Boric Acid					NF
Sodium Citrate (b) (4) (b) (4)					USP
Sodium Chloride					USP
Water for Injection¥					USP
(b) (4)					
(b) (4)					

(b) (4)

[redacted]

Note: We would like to inform the Agency that we have received agency's confirmation w.r.t. Q1 and Q2 sameness of our drug product with the reference listed drug, PRED FORTE® (prednisolone acetate ophthalmic suspension USP) 1%. Please refer the Agency's Correspondence Response (#37229) dated August 04, 2021 to our Controlled Correspondence dated June 23, 2021. We have used (b) (4) as proposed in above controlled correspondence.

Table 4: IIG Limits for the Excipients Used in the Drug Product

Ingredient [Grade]	Maximum Amount in mg per mL [unit dose]	Quantity per Dosage Unit (%w/w)/ (%w/v)	Maximum amount in mg per mL based on Maximum Daily Dose (MDD) (%)	Recommended IID Levels (%w/v) (Ophthalmic Route)	Reference to Standards
Benzalkonium Chloride (b) (4) (b) (4)	[redacted]			(b) (4)	NF
Edetate disodium (b) (4)					USP
Polysorbate 80					NF
Sodium Bisulfite					IH
Hypromellose USP (b) (4) (b) (4)					USP
Boric Acid					NF
Sodium Citrate (b) (4) (b) (4) USP (b) (4)					USP
Sodium Chloride					USP

IID - Inactive Ingredient Database; (b) (4)

(b) (4)

[redacted]

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3.2.P.3.2 Batch Formula [PRED FORTE® Ophthalmic Suspension]

(b) (4)

Table 1 Quantitative Composition for the Drug Product

Ingredients	Reference to Standards	Concentration (% w/v)	Concentration (mg/mL)
Prednisolone Acetate	USP / Ph. Eur	(b) (4)	
Benzalkonium Chloride[1]	NF / Ph. Eur		
Edetate Disodium	USP / Ph. Eur		
Boric Acid	NF / Ph. Eur		
Sodium Citrate, (b) (4)	USP / Ph. Eur		
Sodium Bisulfate	FCC		
Sodium Chloride	USP / Ph. Eur		
Polysorbate 80[2]	NF / Ph. Eur		
Hypromellose	USP / Ph. Eur		
Purified Water	USP / Ph. Eur		

(b) (4)

****

Prednisolone acetate – *(PSG Draft Guidance)*:
"Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentration as the RLD. For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulation for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."

Drug Substance:
Prednisolone acetate, USP (micronized, (b) (4) is used by the ANDA applicant.

(b) (4)

(b) (4)

Inactive Ingredients' Quality (Q1):
The DP is Q1 same with respect to the RLD (b) (4)

DP composition (Q2):
As per CC # 37229, the agency acknowledged (correspondence receipt date: 6/23/2021; correspondence response date: 8/4/2021) that "OGD would not likely refuse to receive an abbreviated new drug application (ANDA)" for the DP composition proposed on June 23, 2021.
"Reference is made to the definition of **quantitative sameness** to the reference listed drug (RLD) as stated in the guidance for industry on ANDA Submissions - Refuse-to-Receive Standards (December 2016, Revision 2)."
The applicant developed one of the two formulations proposed in the correspondence dated June 23, 2021.

Table: Evaluation of quantitative sameness (Q2)

Ingredients	DP formulation (% w/v)	RLD (% w/v) [not for FOIA] (b) (4)	Assessor comments
Prednisolone Acetate	1.00		Q2 comparable
Benzalkonium Chloride	0.038		Q2 comparable
Edetate Disodium	0.0127		Q2 same
Boric Acid	0.96		Q2 comparable
Sodium Citrate, (b) (4)	0.29		Q2 comparable
Sodium Bisulfite	0.062		Q2 comparable
Sodium Chloride	0.26		Q2 comparable
Polysorbate 80	0.0538		Q2 comparable[1]
Hypromellose	0.12		Q2 same
WFI	q.s.		Q2 comparable

(b) (4)

Assessment: ***{N/A}***
Refer to review of 3.2.P.5.3.

Comparability Protocols

Assessment: ***{N/A}***
No Comparability Protocols are proposed.

Lifecycle Management Considerations

N/A

DRUG PRODUCT LIST OF DEFICIENCIES (R01a, CRL)

(b) (4)

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(b) (4)

Primary Drug Product Assessor Name and Date: Shirshendu Deb, 8/22/2022, 8/26/2022. 11/08/2022, 11/10/2022 (R01a, CRL)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yongeng (Frank) Yao, 25Agu2022, 26Aug2022. Yili Li, 11/10/2022

CHAPTER III: ENVIRONMENTAL

For more details about the items in this template, please see Chapter III (Environmental) of the ANDA IQA Guide

R REGIONAL INFORMATION

Environmental

Assessment: ***{Adequate}***
The applicant has submitted Categorical Exclusion claim under 21 CFR 25.31(a) and a statement certifying compliance with 21 CFR 25.15(d).

Primary Environmental Assessor Name and Date: Shirshendu Deb, 8/26/2022, 11/08/2022 (R01a, CRL).

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yili Li,

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the ANDA IQA Guide

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)? _____

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:

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

Assessment (R#01): in-use stability study is pending. (b) (4)

If "No," explain.

For OTC Drugs and Controlled Substances:

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:

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None (R#01)

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

R#01: None

Primary Drug Product Assessor Name and Date: Shirshendu Deb, 8/22/2022, 8/26/2022, 11/08/2022.

Secondary Drug Product Assessor Name and Date: Yongneng (Frank) Yao, 25Aug2022, 26Aug2022. Yili Li, 11/10/2022

R REGIONAL INFORMATION

Comparability Protocols

Assessment: *{Adequate/Inadequate}*

Lifecycle Management Considerations

N/A

Yili Li

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GUID: 57573c63003677e420bfae1fb7770d72

Shirshendu Deb

Digitally signed by Shirshendu Deb
Date: 11/10/2022 11:47:46AM
GUID: 617aac23007c0baef3c826610ebf0887

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 216935
Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP (5mL, 10mL, 15mL)
Strengths	1%
Dosage Form	Suspension
Administration Route	Ophthalmic
Indication	Prednisolone Acetate Ophthalmic Suspension USP, 1% is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Applicant Name	Lupin Limited
RLD Number	N017011
Primary Assessor	Andrew Idzior
Secondary Assessor	Sateesh Sathigari

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate - Major
THEME: Inadequate Facility - cGMP Withhold
JUSTIFICATION: The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.
Process Assessment Recommendation: Inadequate - Minor

Assessment Summary:

Facilities: Withhold is recommended due to unacceptable OAI compliance status of both the DS and DP manufacturing sites due to GMP inspections results.

Pre-approval inspection of the Lupin (FEI: 3007549629) (b) (4) manufacturing facility is also needed once the compliance status is resolved. The facility does not have a history of manufacturing suspensions. The other facilities (lab testing sites) proposed are acceptable.

Process: Withhold is recommended. The risks of the proposed manufacturing operations are not fully mitigated by the development data, exhibit batch data, and process controls. (b) (4)

Product Description:

1.0 DESCRIPTION OF DOSAGE FORM

Table 1: Description of the Drug Product

Fill Volume	Description
5 mL [redacted] 10 mL round opaque white [redacted] bottle)	White to off-white milky fine suspension filled in opaque white bottle closed with opaque white nozzle and then with white cap.
10 mL [redacted] 15 mL round opaque white [redacted] bottle)	
15 mL [redacted] 5 mL round opaque white [redacted] bottle)	

Dosage:

DOSAGE AND ADMINISTRATION

Shake well before using. Instill one to two drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosing frequency may be increased if necessary. Care should be taken not to discontinue therapy prematurely.

[redacted]

Process Description:

[redacted]

3.0 INTENDED COMMERCIAL BATCH MANUFACTURING RECORDS AND PACKAGING RECORDS

[redacted]

Product	Fill Volume	Exhibit Batch Size	Intended Commercial Batch Size	Scale Up
Prednisolone Acetate Ophthalmic Suspension USP 1%	5 mL in 10 mL [redacted] Bottle	[redacted]		
	10 mL in 15 mL [redacted] Bottle			
	15 mL in 15 mL [redacted] Bottle			

Following intended commercial batch production records are provided under in this section.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received

PFC (SD 1)	01/21/2022
Original Submission (SD 2)	04/11/2022
Request for SEPT 14, 2022, Mid-Cycle Meeting (SD 3)	06/08/2022
Response to Micro IR (SD 5)	08/26/2022
Response to Quality IR (SD 9)	10/07/2022

Additional Submissions:

Document Description (SD #)	Date Received
Response to Biopharm IR (SD 4)	07/28/2022
Response to Clinical IR (SD 6)	09/01/2022
Response to Labeling IR (SD 7)	09/02/2022
Response to Bioequivalence (SD 8)	09/19/2022

Highlight Key Issues from Last Cycle and Their Resolution: NA

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

- The applicant does not account for [redacted] (b) (4)
- [redacted] (b) (4) Additional process development data may be required.
- Surveillance inspections found [redacted] (b) (4) and the [redacted] (b) (4), Lupin Limited (FEI: 3007549629), manufacturing facilities to be unacceptable.

List Number of Comparability Protocols:

1. Lifecycle Management Considerations

Post-approval inspection?	Yes. #PoAI. Facility Name/FEI:
Lifecycle considerations	Choose an item.
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
[redacted] (b) (4)			Withhold - Based on CGMP

(b) (4)			Approve - Based on Previous History
M/s. Lupin Limited (Drug Product Manufacturing Site) Unit-2, Plot No. M-2 and M-2-A, Special Economic Zone, Phase - II, Misc. Zone Apparel Park, Dist- Dhar, , Pithampur, Madhya Pradesh, India, 454775	3007549629	(b) (4)	Withhold - Based on CGMP Pre-approval inspection of the Lupin (FEI: 3007549629) drug product manufacturing facility is also needed once the compliance status is resolved.
M/s. Lupin Limited Unit-3, Plot No. M-1 and M-3-A, Special Economic Zone, Phase – II, Misc. Zone Apparel Park,, Pithampur, Madhya Pradesh, India, 454775	3009107538		Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History

II. Drug Product Manufacturing

(b) (4)

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Request for Additional Information (#RAI) and Response	
Outcome	Choose an item.

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
(b) (4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Andrew Idzior	Sateesh Sathigari	9/5/2022	IR	Withheld
2	Andrew Idzior	Sateesh Sathigari	11/7/2022	CR Minor	Withheld
Choose an item.			Click to enter a date.	Choose an item.	Choose an item.

Andrew Idzior

Digitally signed by Andrew Idzior
Date: 11/07/2022 01:19:25PM
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Sateesh Kumar Sathigari

Digitally signed by Sateesh Kumar Sathigari
Date: 11/08/2022 10:06:40AM
GUID: 5527d5b90078ffc994fda2663285a190

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 216935

Drug Product: PREDNISOLONE ACETATE

DMF#: (b) (4)

DMF Subject (API name): PREDNISOLONE ACETATE USP

DMF Holder: (b) (4)

Note: If the DMF is for a mixture of the API and excipient(s) (e.g. stabilizer, buffer), email DMF OGD Mailbox (DMFOGD@fda.hhs.gov) and include the URL to the project; example "this TCIR is for an API excipient mixture".). Note to reviewer: Do not archive the TCIR document as changes may need to be made.

1. Are there any **secondary DMFs** referenced by this DMF? ☒**Yes** ☐No
   If yes, fill in the following table.

Secondary DMF #	Subject of the DMF	Intermediate/Starting material?
(b) (4)	(b) (4)	(b) (4)
(b) (4)		

Note: If the secondary DMF is for a regulatory starting material, a review of the secondary DMF may not be needed.

2. **For original DMFs only: Is the regulatory starting material appropriately designated as per ICH Q11 guidelines?** ☒**Yes** ☐No ☐N/A
   If No, has the firm provided complete facility information?
   ☐Yes. Fill in the following table and send a directed update to the RBPM under the most recent DMF project in Panorama. Use IR comment #1 in TCIR-IR Comments template (SharePoint: DLAPI/TCIR/TCIR-IR Comments).

☐No. Fill in what has been provided and send a directed update to the RBPM under the most recent DMF project in Panorama for missing information. Use IR comment in #2 in TCIR-IR Comments template (SharePoint: DLAPI/TCIR/TCIR-IR Comments).

Facility Name and Address#	FEI/DUNS	Intermediate critical (Y/N)**	Justification*

* Re-designation of the KSM may result in a starting material facility becoming an intermediate manufacturing facility, therefore please select a justification(s) from the following:

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.

2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

4. Intermediate is not deemed critical because the criteria above do not apply.

5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

Note: Add "Pending Evaluation" as the initial assessment. Update this once the response to IR is received.

Note: If intermediate facility is not deemed critical, the facility IR comment is NOT issued to the ANDA applicant.

3. Are there any intermediate facilities **listed in the 356h**? ☐Yes ☒**No**

If yes, determine if the intermediate facility is critical.

Facility Name and Address	FEI/DUNS	Intermediate critical (Y/N)	Justification*

* If an intermediate facility is identified, please select justification(s) from the following:
  1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.
  2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.
  3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.
  4. Intermediate is not deemed critical because the criteria above do not apply.
  5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

4. Does the Type II API DMF list any manufacturing facilities, intermediate facilities, or testing facilities for routine release or stability testing that are **not listed in the facility profile and/or on the 356h** form for the referencing ANDA? ☐Yes ☒**No**

If yes, include the information identifying each facility and its function below:

Facility Name and Address#	**Function$**	**Justification if Intermediate facility***	**FEI/DUNS#**

* If an intermediate facility is identified, please select justification(s) from the following:
  1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.
  2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.

4. Intermediate is not deemed critical because the criteria above do not apply.

5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre- existing facility and was not evaluated for other applications.

Note: If intermediate facility is not deemed critical, the facility IR comment is NOT issued to the ANDA applicant.

$ Facility function codes for hidden and critical intermediate facilities:

CSN: Non-Sterile API by Chemical Synthesis
CSS: Sterile API by Chemical Synthesis
CSP: Chemical Sterilization
LCP: Laboratory, Chemical/Physical Testing
LBI: Laboratory, Biological Testing
LMS: Laboratory, Microbiological – Sterility Testing
LMN: Laboratory, Microbiological – Non-Sterility Testing
CXA: Plant/Animal Extraction Purified API
CFN: Non –Sterile API by Fermentation
CFS: Sterile API by Fermentation
CRU: API Non-Sterile/Intermediate (***Note: The only code to be used for the intermediate facilities***)

#***Note:*** *Not for FOI boxes (refer to SOP for format) need to be used if the facility information is submitted in a secondary DMF.*

Note to Reviewer: Do not alter this language beyond providing the specifics for the yellow and blue text.

DMF hidden facility language to be issued to ANDA applicant if the site is in primary or secondary DMF:
-N/A.

5. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult?
☐Yes ☒**No**

If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

Consult form date:

6. After examining the labelling for the drug product:

Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐Yes ☒**No**

Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐Yes ☒**No**

TCIR Note: *MDD and duration of use was deermined by DPTR in a consult sent for DMF* (b) (4) (https://panorama.fda.gov/task/view?ID=601b1b2c00420a70ca0de30203600435)

Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐Yes ☒**No** ☐N/A

Is a DCR consult required to determine that the drug substance is carcinogenic? ☐Yes ☒**No**

If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

Consult form date:

David Green

Digitally signed by David Green
Date: 5/04/2022 07:45:10PM
GUID: 508da70400028936e7195eb2fb140e89

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216935

BIOEQUIVALENCE REVIEW(s)

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	ANDA 216935-ORIG-1-Amend-012
Product Name	Prednisolone Acetate Ophthalmic Suspension, USP, 1%
Applicant	Lupin Limited
Dosage Form	Ophthalmic Suspension
Route of Administration	Topical
Intended Use	For the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Submission Date	01/21/2022, Original submission 07/28/2022, Response to Information Request (dated 06/28/2022) 12/07/2022, Complete Response Letter 10/17/2023, Response to Complete Response Letter 01/05/2024, Response to Information Request (dated 12/21/2023) 05/10/2024 (SDN 12), Response to Complete Response Letter (dated 04/04/2024)
RLD	PRED FORTE (Prednisolone Acetate Suspension/Drops; Ophthalmic, 1%) [NDA 017011, approved prior to 01/01/1980]
Primary Reviewer	Parnali Chatterjee, Ph.D.
Recommendation	**ADEQUATE**

EXECUTIVE SUMMARY:

The objective of this assessment is to evaluate the Applicant's response to the Biopharmaceutics deficiencies conveyed in the Information Request (IR) comment (dated 12/21/2023).

Two in vitro release methods, a quality control (QC) batch release method [(b) (4)] and an in vitro release test [(IVRT), *USP App 4 (flow through cell closed loop) using 150 mL phosphate buffer, pH 5.5 at 8.0 mL/min at 35°C*] were proposed (see **Table 1a**) in the original submission (dated 04/11/2022) to support in vitro bioequivalence (BE) for the proposed Prednisolone Acetate Ophthalmic Suspension, USP, 1% product.

In the IR comment (dated 06/28/2022) the Applicant was recommended the QC release method to support in vitro BE of the proposed product. However, based on additional physico-chemical characteristics of the drug product (such as viscosity and particle size distribution (PSD)), the Applicant was recommended to implement the IVRT [*USP App 4 (flow through cell closed loop) using 150 mL phosphate buffer, pH 5.5 at 8.0 mL/min at 35°C*] and '*NMT* (b) (4) *% in 10 minutes and NLT* (b) (4) *% (Q) in 60 minutes*' as the acceptance criteria (see **Table 1b**) for the proposed product in the Complete Response Letter (CRL)[1, 2] (dated 12/07/2022).

[1] Biopharm Review_Original; [2] Complete Response Letter

In the CRL response (dated 10/17/2023), the Applicant agreed to implement the IVRT and proposed a new set of acceptance criteria for the drug product that would not reject the IVRT data for the variant batches. Hence, a new set of acceptance criteria '*NLT* (b)(4) *% in 10 minutes and NLT* (b)(4) *% (Q) in 60 minutes*' at *Stage 2* testing was conveyed to the Applicant in the IR comment (dated 12/21/2023)[3].

In a subsequent IR response (dated 01/05/2024) and CRL response (dated 05/10/2024), the Applicant agreed to implement the newly recommended acceptance criteria and provided IVRT data for the exhibit batches of the drug product that would meet the recommended acceptance criteria on long-term stability at 24 months.

Recommendation:
From Biopharmaceutics perspective, the ANDA 216935-ORIG-1-Amend-012 for Prednisolone Acetate Ophthalmic Suspension, USP, 1% is recommended for **APPROVAL**.

The approved IVRT and acceptance criteria for in vitro release testing of Prednisolone Acetate Ophthalmic Suspension, USP, 1% are as follows:

In Vitro Release Specification				
Purpose	**Apparatus**	**Temperature**	**Medium / Volume (ml)**	**Acceptance Criteria**
To support QC batch release and in vitro bioequivalence (BE)	USP App 4 (flow through cell closed loop), at 8.0 mL/min	35°C	Phosphate buffer, pH 5.5 - Volume: 150 mL	NLT (b)(4)% in 10 minutes and NLT (b)(4) (Q) in 60 minutes

[3] Biopharm Review 2

REVIEWER'S ASSESSMENT

In the original submission (dated 04/11/2022), a quality control (QC) batch release method [(b) (4) *C*] and an in vitro release test [(IVRT), *USP App 4 (flow through cell closed loop) using 150 mL phosphate buffer, pH 5.5 at 8.0 mL/min at 35°C*] were proposed (see **Table 1a**) to support in vitro bioequivalence (BE) for the proposed Prednisolone Acetate Ophthalmic Suspension, USP, 1% product. Based on the overall data provided in the submission, the Applicant was recommended to implement the QC release method to support in vitro BE of the proposed product in the IR (dated 06/28/2022).

In response[1] (dated 07/28/2022) to an IR (dated 06/28/2022), viscosity and particle size distribution (PSD) were proposed as alternatives to IVRT for batch release and stability testing of the commercial batches and IVRT was proposed to support in vitro BE, which was deemed inadequate. The Applicant was recommended to propose the IVRT and '*NMT (b) (4)% in 10 minutes and NLT (b) (4)% (Q) in 60 minutes*' as the acceptance criteria (see **Table 1b**) for the proposed product in the CRL (dated 12/07/2022)[2].

Table 1a. Originally and newly proposed quality control (QC) batch release method and in vitro release test (IVRT) for Prednisolone Acetate Ophthalmic Suspension, USP, 1% product

In Vitro Release Specification						
	Purpose	Apparatus	Rotation Speed	Temperature	Medium / Volume (ml)	Acceptance Criteria
1	(b) (4)					(b) (4)
2	IVRT: To support in vitro bioequivalence (BE)	USP App 4 (flow through cell closed loop), at 8.0 mL/min		35°C	Phosphate buffer, pH 5.5 - Volume: 150 mL	(b) (4) New NMT (b) (4)% in 10 mins NLT (b) (4)% in 60 mins

Table 1b. Recommended in vitro release test for Prednisolone Acetate Ophthalmic Suspension, USP, 1% product

In Vitro Release Specification				
Purpose	**Apparatus**	**Temperature**	**Medium / Volume (ml)**	**Acceptance Criteria**
To support QC batch release and in vitro bioequivalence (BE)	USP App 4 (flow through cell closed loop), at 8.0 mL/min	35°C	Phosphate buffer, pH 5.5 - Volume: 150 mL	NMT (b)(4)% in 10 minutes and NLT (b)(4)% (Q) in 60 minutes

In the CRL response (dated 10/17/2023), the Applicant agreed to implement the IVRT [*USP App 4 (flow through cell closed loop) using 150 mL phosphate buffer, pH 5.5 at 8.0 mL/min at 35°C*] to support in vitro BE, for batch release of the proposed product. However, a new acceptance criteria '*NMT (b)(4)% in 10 minutes and NLT (b)(4)% (Q) in 60 minutes*' was proposed for the drug product. Comparative IVR data were provided for three exhibit batches of the proposed product and the RLD using the recommended IVRT to support the newly proposed acceptance criteria (see **Table 2**).

Table 2. Comparative IVR data for three exhibit batches of the proposed product and the RLD using the recommended IVRT at *Stage 2* testing

Dissolution Condition	**Batch No / Lot No.**	**Mfg. Date / Expiry Date**	**% Drug Release Avg (Min-Max)**	
			10 min	**60 minutes**
Apparatus: USP IV (Closed Loop)	H190066	June 2021	50 (b)(4)	91 (b)(4)
	H190067	June 2021	54	93
	H190068	June 2021	50	85
Media: Phosphate Buffer pH 5.5, 150 mL at 35 °C at 8.0 mL/min.	08632	April 2022	51	92
	09116	July 2022	50	93
	09634	September 2022	50	88

The IVR data for one exhibit batch H190066 of the proposed product manufactured in June 2021 demonstrated high variability (b)(4)%) at 10 minutes and would not meet the recommended acceptance criteria '*NMT (b)(4)% in 10 minutes and NLT (b)(4)% (Q) in 60 minutes*' at *Stage 2* testing. However, the batch would meet the newly proposed acceptance criteria '*NMT (b)(4)% in 10 minutes*' at *Stage 2* testing.

Table 3. IVRT data for variant batches of the drug product

Upon assessment of the IVRT data for the variant batches of the drug product manufactured with (b) (4) (see **Table 3**), it was observed that the data would not be rejected by the recommended and newly proposed acceptance criteria at 10 minutes. However, if the Applicant implemented '*NLT (b) (4)% in 10 minutes and NLT (b) (4)% (Q) in 60 minutes*' at *Stage 2* testing, the variant batches could be rejected by the newly recommended acceptance criteria. Hence, in the Information Request comment (dated 12/21/2023), the Applicant was recommended a new set of acceptance criteria[3].

In the IR response (dated 01/05/2024) and CRL response (dated 05/10/2024), the Applicant agreed to implement the recommended acceptance criteria for IVRT of the proposed drug product. In vitro release data for all exhibit batches of the drug product will meet the recommended acceptance criteria on long-term stability at 24 months.

Considering the overall information provided in the response, the following IVRT and acceptance criteria are approved for in vitro release testing of Prednisolone Acetate Ophthalmic Suspension, USP, 1%.

In Vitro Release Specification			
Purpose	**Apparatus**	**Medium / Volume (ml)/ Temperature**	**Acceptance Criteria**
To support QC batch release and in vitro bioequivalence (BE)	USP App 4 (flow through cell closed loop), at 8.0 mL/min	Phosphate buffer, pH 5.5 - Volume: 150 mL/35°C	NLT (b) (4)% in 10 minutes and NLT (b) (4)% (Q) in 60 minutes

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	ANDA 216935-ORIG-1-Amend-010
Product Name	Prednisolone Acetate Ophthalmic Suspension, USP, 1%
Applicant	Lupin Limited
Dosage Form	Ophthalmic Suspension
Route of Administration	Topical
Intended Use	For the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Submission Date	01/21/2022, Original submission 07/28/2022, Response to Information Request (dated 06/28/2022) 12/07/2022, Complete Response Letter 10/17/2023, Response to Complete Response Letter
RLD	PRED FORTE (Prednisolone Acetate Suspension/Drops; Ophthalmic, 1%) [NDA 017011, approved prior to 01/01/1980]
Primary Reviewer	Parnali Chatterjee, Ph.D.
Recommendation	**INADEQUATE** Minor

EXECUTIVE SUMMARY:

The objective of this assessment is to evaluate the Applicant's response to the Biopharmaceutics deficiencies conveyed in the Complete Response Letter (CRL) dated 12/07/2022.

In the original submission (dated 04/11/2022), a quality control (QC) batch release method (b) (4) and an in vitro release test [(IVRT), *USP App 4 (flow through cell closed loop) using 150 mL phosphate buffer, pH 5.5 at 8.0 mL/min at 35°C*] to support in vitro bioequivalence (BE) were proposed (see **Table 1a**) for the proposed Prednisolone Acetate Ophthalmic Suspension, USP, 1% product. Based on the overall data provided in the submission, the Applicant was recommended to propose the QC release method to support in vitro BE of the proposed ophthalmic suspension in the *Information Request* (IR dated 06/28/2022).

The Applicant proposed viscosity and particle size distribution (PSD) as alternatives to the IVRT for batch release and stability testing of the commercial batches and IVRT to support in vitro BE in the IR response[1] (dated 07/28/2022), which was deemed inadequate. The Applicant was recommended to propose the IVRT and '*NMT (b) (4)% in 10 minutes and NLT (b) (4)% (Q) in 60 minutes*' as the acceptance criteria (see **Table 1b**) for the proposed product in the Complete Response Letter (dated 12/07/2022).

[1] Response (07/28/2022) to Information Request \\CDSESUB1\EVSPROD\anda216935\0004\m1\us\response-to-deficiencies.pdf

Table 1a. Originally and newly proposed quality control (QC) batch release method and in vitro release test (IVRT) for Prednisolone Acetate Ophthalmic Suspension, USP, 1% product

In Vitro Release Specification						
Purpose		Apparatus	Rotation Speed	Temperature	Medium / Volume (ml)	Acceptance Criteria
[redacted]						(b) (4)
2	To support in vitro bioequivalence (BE)	USP App 4 (flow through cell closed loop), at 8.0 mL/min		35°C	Phosphate buffer, pH 5.5 - Volume: 150 mL	(b) (4)
						New NMT (b) (4)% in 10 mins NLT (b) (4)% in 60 mins

Table 1b. Recommended in vitro release test for Prednisolone Acetate Ophthalmic Suspension, USP, 1% product

In Vitro Release Specification				
Purpose	Apparatus	Temperature	Medium / Volume (ml)	Acceptance Criteria
To support QC batch release and in vitro bioequivalence (BE)	USP App 4 (flow through cell closed loop), at 8.0 mL/min	35°C	Phosphate buffer, pH 5.5 - Volume: 150 mL	NMT (b) (4)% in 10 minutes and NLT (b) (4)% (Q) in 60 minutes

In the CRL response (dated 10/17/2023), the Applicant agreed to implement the IVRT [*USP App 4 (flow through cell closed loop) using 150 mL phosphate buffer, pH 5.5 at 8.0 mL/min at 35°C*] used to support in vitro BE, for batch release of the proposed product. However, the Applicant proposed a new acceptance criteria '*NMT (b) (4)% in 10 minutes and NLT (b) (4)% (Q) in 60 minutes*' for the proposed product. To support the newly proposed acceptance criteria, the Applicant provided comparative IVR data for three exhibit batches of the proposed product and the RLD using the recommended IVRT (see **Table 2**).

The IVR data for one exhibit batch H190066 of the proposed product manufactured in June 2021 demonstrates high variability ([b) (4)]%) at 10 minutes and would not meet the recommended acceptance criteria '*NMT* [b) (4)]*% in 10 minutes and NLT* [b) (4)]*% (Q) in 60 minutes*' at *Stage 2* testing. However, the batch would meet the newly proposed acceptance criteria '*NMT* [b) (4)]*% in 10 minutes*' at *Stage 2* testing.

Table 2. Comparative IVR data for three exhibit batches of the proposed product and the RLD using the recommended IVRT at *Stage 2* testing

Dissolution Condition	Batch No / Lot No.	Mfg. Date / Expiry Date	% Drug Release Avg (Min-Max)	
			10 min	60 minutes
Apparatus: USP IV (Closed Loop)	H190066	June 2021	50 [b) (4)]	91 [b) (4)]
	H190067	June 2021	54	93
	H190068	June 2021	50	85
Media: Phosphate Buffer pH 5.5, 150 mL at 35 °C at 8.0 mL/min.	08632	April 2022	51	92
	09116	July 2022	50	93
	09634	September 2022	50	88

[b) (4)]

Based on the IVRT data, the Applicant will be recommended to implement '*NLT* [b) (4)]*% in 10 minutes and NLT* [b) (4)] *(Q) in 60 minutes*' at *Stage 2* testing.

Table 3. IVRT data for variant batches of the drug product

[b) (4)]

Recommendation:
From Biopharmaceutics perspective, the approvability of ANDA 216935-ORIG-1-Amend-010 for Prednisolone Acetate Ophthalmic Suspension, USP, 1% is pending due to outstanding Information Request comment.

Deficiency to be conveyed to the Applicant:

1. We noticed you proposed a new in vitro release (IVR) acceptance criteria '*NMT* [(b) (4)] *% in 10 minutes and NLT* [(b) (4]] *(Q) in 60 minutes*' for IVR testing of Prednisolone Acetate Ophthalmic Suspension, USP, 1% using *USP App 4 (flow through cell closed loop), at 8.0 mL/min in 150 mL phosphate buffer, pH 5.5 at 35°C*. However, the proposed acceptance criteria will not be able to reject the variant batches PRS/2086/136, PRS/2086/137, and PRS/2086/138 [(b) (4)] as the acceptance criteria for the product, all three variant batches will be rejected by the recommended acceptance criteria at 10 minutes. Therefore, we request that you implement the recommended acceptance criteria '*NLT* [(b) (4)] *% in 10 minutes and NLT* [(b) (4)] *(Q) in 60 minutes*' for IVRT of Prednisolone Acetate Ophthalmic Suspension, USP, 1%.

   Please update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	ANDA-216935-ORIG-1
Product Name	Prednisolone Acetate Ophthalmic Suspension
Applicant	Lupin Limited
Dosage Form/Strengths	Suspension, 1% (5 mL)
Route of Administration	Ophthalmic
Indication for Use	It is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Submission Date	4/11/2021
Review Date	8/26/2022
Primary Reviewer	Min Sung Suh, Ph.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	**Inadequate-major**

EXECUTIVE SUMMARY

***Background and Submission*:**
The proposed product, Prednisolone Acetate Ophthalmic Suspension, 1% (5 mL) referenced the Reference Listed Drug (RLD), PRED FORTE® (Prednisolone acetate Ophthalmic Suspension), 1% that was developed by Allergan Pharmaceutical and approved by the FDA under NDA 017011 on 5/30/1973. Lupin Limited proposes a generic version of Prednisolone Acetate Ophthalmic Suspension, 1% (5 mL), and this ANDA submission was granted as a Competitive Generic Therapy (CGT) on 3/15/2022 under section 505 H(b).

***Review's Objective*:**
The Biopharmaceutics assessment focuses on the evaluation of the *in vitro* release test (IVRT) method for quality control of the proposed product and the acceptance criteria for the proposed drug product.

Review Summary:
ANDA-216935-ORIG-1, seeking approval of Prednisolone Acetate Ophthalmic Suspension, 1% (5 mL) was submitted on 4/11/2022 for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe. The Prednisolone Acetate API is a low-solubility compound. The Applicant proposes the in vitro studies option to demonstrate bioequivalence (BE) to the RLD which encompasses a comparable in vitro drug release of the proposed drug product to the RLD.

To demonstrate BE and ensure QC of the proposed product, the Applicant developed two in-house IVRT methods to quantify the release of the prednisolone acetate. Due to inadequate information in the IVRT method development for the proposed QC method, an Information Request (IR) was conveyed to the Applicant dated 06/28/2022, and in a response to the IR comments dated 07/28/2022, the Applicant provided additional justification and data to support the proposed IVRT method for quality control of the product. The Applicant stated that with defined manufacturing process and tight controls for PSD and viscosity, dissolution/drug release is unlikely to be impacted.

Based on the assessment of the provided information, there is no strong evidence to support discriminating ability of the proposed QC method towards CQAs as identified in the IVRT used for BE. Considering that the IVRT method for BE is more discriminating towards CMA (particle size) and CFV (HPMC level: viscosity) than the proposed method for quality control of the proposed product the method used for BE should be considered as QC method, the recommendation will be conveyed to the Applicant via DRL.

CONCLUSION:

From a Biopharmaceutics perspective, ANDA-216935-ORIG-1 is **PENDING** due to comments listed below.

Biopharmaceutics Information Request:

We acknowledge the response to the IR comments dated 07/28/2022. We found your proposed in vitro release test (IVRT) method not acceptable for quality control of your proposed drug product, Prednisolone acetate Ophthalmic Suspension, 1%.

We recommend that the IVRT method [i.e., the method used to demonstrate in vitro bioequivalence (BE)] is adopted for Quality Control (QC) testing of your proposed drug product. Adopting a single method for BE demonstration and QC of the product enables the identification and rejection of variant batches of unacceptable quality (e.g., non-BE batches), based on the release profile comparison and appropriate establishment of the acceptance criterion(a).

Therefore, based on the totality of the submitted information, we recommend that the following IVRT method and acceptance criteria for QC of the product:

IVRT method: 150 mL of pH 5.5 Phosphate Buffer @35°C/USP IV (Flow through cell-closed loop) at 8.0 mL/min

Acceptance criteria: NMT (b)(4)% in 10 minutes and NLT (b)(4)% (Q) in 60 minutes

Implement the recommended IVRT method and acceptance criteria and update the drug product release and stability specifications, and other parts of your ANDA submission, accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised release acceptance criteria in your stability program through your proposed expiry period. If drug release failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures.

1. SUBMISSION CONTENT CHECKLIST:

	INFORMATION	YES	NO	N/A
1	Is there a USP dissolution method?	☐	☒	☐
2	Did the Applicant use the USP dissolution method?	☐	☐	☒
3	Is there an FDA-Database dissolution method?	☐	☒	☐
4	Did the Applicant use the FDA-Database dissolution method?	☐	☐	☒
5	Did the Applicant conduct dissolution testing with a proposed in-house dissolution method?	☒	☐	☐
6	Did the Applicant use 12 individual units of the test (proposed) drug product in the dissolution testing?	☒	☐	☐
7	Did the Applicant provide complete dissolution data for the test (proposed) drug product (all raw data, range, mean, % CV, date of dissolution testing)?	☒	☐	☐
8	Was the dissolution/release testing and pivotal bioequivalence study conducted using test drug product within the proposed expiry period?	☒	☐	☐
9	Does the proposed product (any strength) have a functional scoring?	☐	☒	☐
10	If there is a functional scoring, did the Applicant provide complete dissolution data for the whole vs. split tablets?	☐	☐	☒
11	Is there significant change in the dissolution of stability samples?	☐	☐	☒

2. BIOPHARMACEUTICS ASSESSMENT:

- ***Solubility Data***: The aqueous solubility profile of the API over the physiological pH range indicates a pH-independent solubility in the range of 0.0106 mg/mL to 0.0122 mg/mL as shown in Table 1. Therefore, the prednisolone acetate can be considered as a low-solubility drug substance. Since the drug product is intended for ophthalmic (topical) administration, BCS classification is not applicable.

Table 1. Solubility of drug substance at multimedia with different pH conditions

S. No.	Dissolution media	Initial pH of media	Final pH of Sample	Solubility (mg/mL)	Solubility (µg/mL)
1	Water	(b) (4)		0.0116	11.648
2	0.1N HCl			0.0122	12.159
3	PH 4.5 Acetate Buffer			0.0118	11.839
4	PH 6.8 Phosphate Buffer			0.0106	10.645
5	PH 7.4 Phosphate Buffer			0.011	10.969
6	PH 7.4 Phosphate Buffer +0.1%SLS			0.013	12.600
7	PH 7.4 Phosphate Buffer +0.5%SLS			0.145	145.1
8	PH 7.4 Phosphate Buffer +0.1% Tween- 80			0.011	11.3
9	PH 7.4 Phosphate Buffer + 0.5% Tween- 80			0.021	21.5

- ***Formulation***: The proposed drug product is Q1/Q2 similar to the RLD (PRED FORTE Ophthalmic Suspension)[1] so as to ensure bioequivalence. (b) (4)

(b) (4)

Table 2. Components and composition of drug product

[1] Link to composition of the proposed drug product

Ingredients [Grade]	1%			Category	Reference to Standards
	Unit Quantity (mg/mL)	%w/v	%w/w		
Prednisolone acetate* $ (sterile, (b) (4)	10.000	(b) (4)	(b) (4)	Active Ingredient	USP
Benzalkonium Chloride (b) (4) (b) (4)	(b) (4)			(b) (4)	NF
Edetate disodium (b) (4)					USP
Polysorbate 80					NF
Sodium Bisulfite*					IH
Hypromellose (b) (4) (b) (4)					USP
Boric Acid					NF
Sodium Citrate (b) (4) (b) (4)					USP
Sodium Chloride					USP
Water for Injection* (b) (4)					USP
					NF

(b) (4)

- ***Dosage, Bioavailability and PK of the RLD***: The recommended dosage is to instill one to two drops into the conjunctival sac(s) two to four times daily (i.e., every six to twelve hours). During the initial 24 – 48 hours, the dosage may be increased if necessary. There is no available data on the extent of systemic absorption of the RLD product.

a) List Submissions being reviewed:

04/11/2022	Original submission/Sequence 0002
07/28/2022	IR response/Sequence 0004

b) In vitro release test (IVRT) method and acceptance criteria proposed by the Applicant:

	Drug release method	
	IVRT for BE	(b) (4)
Apparatus	IV (Flow through cell-closed loop)	
Medium	Phosphate buffer pH 5.5	
Volume	150 mL	
Temperature	35.0°C ± 0.5°C	
Speed (flow)	8.0 mL/min	
Acceptance criterion	(b) (4)	

3. **REVIEWER'S ASSESSMENT:**

***In vitro release test (IVRT) method for BE*:**

To establish bioequivalence (BE) to the RLD/RS, the *Draft Guidance* on Prednisolone acetate Ophthalmic Suspension[2] recommends two options – an *in vitro* studies option and an *in vivo* studies option. The *in vitro* studies option recommends a comparable in vitro drug release for the proposed drug product to the RLD/RS. Although there is a USP monograph for Prednisolone acetate Ophthalmic Suspension, there is no IVRT method in the monograph. The FDA dissolution methods database directs the Applicant to develop a method to characterize the in vitro drug release for the proposed drug product. (b) (4) (b) (4)

The Applicant proposed an in-house IVRT method for BE and provided method development and validation reports. To demonstrate discriminating ability of the IVRT method, the Applicant provided comparative drug release studies using the variant batches (b) (4) . The Applicant stated that the IVRT method is discriminatory since the drug release results showed that the batches (b) (4) (PRS/2086/131B), (b) (4) (PRS/2086/138), (b) (4) (PRS/2086/137), and (b) (4) (PRS/2086/136) have dissimilar drug release profiles compared to the batches (H190066, H190067, and H190068) used for BE studies (Table 3). (b) (4) .

Table 3. Comparative drug release profiles of drug product with different formulation and process variable

[2] Draft Guidance on Prednisolone acetate Ophthalmic Suspension, 1%

***In vitro release test (IVRT) method for QC*:**

In response to the IR comments dated 7/28/2022, the Applicant stated that USP II (Paddle) method was developed for QC (b) (4) In the original submission, the Applicant included method development and validation reports to support adequacy of the proposed method and provided comparative drug release data. (b) (4) Batch #PRS/2086/129A) (b) (4) Batch #PRS/2086/130A) have a (b) (4) compared to the final formulation (P2441B12) as the same drug release trend in the USP IV apparatus (Table 4). However, the variations in the batches used for the comparative drug release studies are considered not meaningful to support discriminating ability of the proposed method (b) (4) .

Based on the submitted information, the proposed OC method is not acceptable due to lack of information demonstrating discriminating ability of the method towards CQAs. Thus, the adequacy of the proposed acceptance criterion of (b) (4) is PENDING at this stage.

Min Sung Suh

Digitally signed by Min Sung Suh
Date: 11/10/2022 10:58:08AM
GUID: 5d418e82002882e44eb53342e324cad8

Om Anand

Digitally signed by Om Anand
Date: 11/10/2022 11:26:23AM
GUID: 508da6fb0002833385a1485d53137893

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	216935	
Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP	
Strength(s)	1%	
Applicant Name	Lupin Limited	
Applicant Address	Off Western Express Highway 3rd Floor, Kalpataru Inspire, Santacruz (East) Mumbai, Maharashtra 400055 India	
US Contact Name and US Mailing Address	Ms. Kalpana Vanam Senior Vice President, Regulatory Affairs Lupin Pharmaceuticals, Inc. 400 Campus Drive Somerset, New Jersey 08873 kalpanavanam@lupin.com	
US Contact Telephone Number	(b) (6) 443-562-6704	
US Contact Fax Number	N/A	
Original Submission Date(s)	04/11/2022	
Submission Date(s) of Amendment(s) Under Review	Response to Discipline Review Letter- 09/19/2022	
Primary Reviewer	Taylor Smith, Ph.D.	
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.	
Tertiary Reviewer	N/A	
Study Number(s)	LBC-21-108	(b) (4) DR/2021/MIR/0010/1.0
Study Type(s)	Drug Particle Size Distribution	In Vitro Release Test
Strength(s)	1%	1%
Clinical Site	N/A	
Clinical Site Address	N/A	
Analytical Site	Lupin Bioresearch Center In Vitro BE Lab	(b) (4)
Analytical Site Address	Lupin Bioresearch Center Invitro BE Lab 46A/47A, Lupin Research Park, Nande Village, Taluka Mulshi Pune – 412 115, Maharashtra, India Ph.: +91-20-66219200	

	Lupin Bioresearch Center Survey No. 146/2/1B, Sai Trinity, Wing - A, Pashan Pune – 411 021, Maharashtra, India Ph.: +91-20-66219200		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)[1]	**Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent)[1]	
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☒ Adequate ☐ Inadequate ☐ N/A		
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	***Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)*** ☒ Recommended/Latest Revision Date: _05/2019; __ RLD Number: __ NDA 017011 _____ ☐ 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, 3, 4, 8	**Formulation Q1/Q2**	**1%**	☒ Adequate ☐Inadequate
1, 3, 4, 8	**Particle Size**	**1%**	☒ Adequate ☐Inadequate

[1] Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

1, 3, 4, 8	**In Vitro Release Test**	**1%**	**☒ Adequate ☐Inadequate**
1, 3, 4, 8	**Waiver/Deem Bioequivalent**	**1%**	**☒ Adequate ☐Inadequate**

Discipline Review Letter (DRL) Response Review

1 EXECUTIVE SUMMARY

This is bioequivalence (BE) assessment of amendment dated 09/19/2022 (supporting document # 8) in response to BE Discipline Review Letter (DRL) dated 08/22/2022.

In the original submission dated 04/11/2022[2], Lupin Limited has requested a waiver of in vivo bioequivalence (BE) testing for its test product, Prednisolone Acetate Ophthalmic Suspension USP, 1% under Section 21 CFR § 320.24(b)(6). The reference listed drug (RLD) and reference standard (RS) is Pred Forte® (prednisolone acetate) Ophthalmic Suspension,1% manufactured by Allergan Pharmaceutical approved under NDA 017011, prior to 01/01/1982[3].

Lupin Limited previously submitted results of particle size distribution (PSD) and in vitro drug release (IVRT) studies comparing the proposed test product, Prednisolone Acetate Ophthalmic Suspension USP, 1% to the corresponding reference product, Pred Forte® (prednisolone acetate) Ophthalmic Suspension, 1%. To support the in vitro option, the applicant submitted all the required in vitro BE studies. However, the requested waiver was not granted, and the application was determined to be inadequate due to deficiencies related to 1) missing method development and optimization report for the PSD study, 2) detailed evaluation of the discriminatory ability of the selected IVRT method, and 3) missing 100% raw data and investigation report for the observed variations (test batch #H190068) and (reference batch # 09634) and rejected runs in the in vitro drug release study.

In the current submission, the applicant provided method development and optimization report for the PSD study, supporting data to show the discriminatory ability of the selected IVRT method and 100% raw data and investigation report for rejected runs in the in vitro drug release study. In response to the DRL, the applicant has adequately addressed the deficiency items listed in the DRL.

OSIS Status "Complete"
Decline to Conduct an On-Site Inspection Memos checked in and OSIS task is complete as shown in the original BE assessment[2]. Please refer to the original BE assessment for details.

The application is **adequate**.

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[2] GDRP. ANDA 216935-ORIG-1 Bioequivalence.
https://panorama.fda.gov/internal/document/preview?versionID=62ffbb97001fd9ba84f9d7bb71494171&ID=62d998e5001ba6a8b814d96dbab0c684
[3] Electronic Orang Book. Search '017011'.
https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product and PK/PD Information

Please refer to original BE review.

4 REVIEW OF CURRENT AMENDMENT

In the Discipline Review Letter dated August 22, 2022, under Division of Bioequivalence the following deficiencies were communicated to the applicant[4]:

Bioequivalence Deficiency #1

Please submit a method development and optimization report for your particle size distribution (PSD) testing to support all your selections of testing conditions/parameters and to justify the appropriateness of your method for PSD testing of Pred Forte® (prednisolone acetate) Ophthalmic Suspension, 1%.

Applicant's Response:
We wish to inform the Agency that the detailed optimized parameters, results and conclusion are presented in Method Optimization Report of Particle Size Distribution as enclosed under the Section "m5-3-1-4-reports-of bioanalytical- and-analytical-methods-for-human-studies".

The finalized method for particle size distribution test is shown as below:

Instrument	(b) (4)
Analytical technique	
Sampling Dispersion Unit	
Method	

Instrument Parameters

[4] ANDA 216935-ORG-1. Bioequivalence DRL.
https://panorama.fda.gov/internal/document/preview?versionID=63037924001adc0ecd545f4c7bcabb50&ID=630378b20027af38df1da8ba1db9b9ba

Measurement Settings	Variable	Value
Particle Type		(b) (4)
Material		
Dispersant		
Measurement		
Sequence		
Sample Dispersion		

Measurement Settings
Data Processing
Output (Data Export)

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

- The applicant submitted the missing method development and optimization report[5] for the selected particle size distribution (PSD) testing. (b) (4) . Unexpired RLD Lot #08632 (also used in original studies) and in house scale up lot #P2441A05 were used for method optimization.
- The method optimization consisted of: selection of instrument, instrument parameters, selection of dispersant medium, optimization of obscuration range and stirrer speed.
- Based on the optimization data provided in the report, the particle distribution sizes obtained for Dv10, Dv50 and Dv90 were consistent and reproducible (b) (4)
- (b) (4)
- The applicant has adequately addressed deficiency comment.

Bioequivalence Deficiency #2

In your in vitro drug release (IVRT) method development and optimization report (No. AMDR/PR47-DR-01/01), your reported f2 similarity values for batches PRS/2086/131B, PRS/2086/136, PRS/2086/137 and PRS/2086/138 were 44, 34, 40 and 37 (f2<50), respectively, demonstrating discriminatory ability; however f2 similarity values (f2>50) for process/formula variation batches PRS/2086/131A, PRS/2086/132, PRS/2086/133, PRS/2086/134 PRS/2086/135A and PRS/2086/135B were all above 50 (i.e., 60, 58, 59, 64, 51 and 70, respectively) and drug release for these batches was found to be comparable to your exhibit batch (H190068). Please explain and clarify discriminatory ability of the IVRT method based on your results.

Applicant's Response:

We wish to inform the Agency that Batches PRS/2086/131B, PRS/2086/136, PRS/2086/137, PRS/2086/138, PRS/2086/131A, PRS/2086/132, PRS/2086/133, PRS/2086/134 and PRS/2086/135A were intentionally manufactured to study the impact of all critical parameters on the dissolution.

The details of the batches manufactured considering the Critical Formulation Variables and Critical Process Parameters along with the results and our assessment are summarized in the below table.

[5] EDR. ANDA 216935. Method Optimization Report. \\CDSESUB1\EVSPROD\anda216935\0008\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\lbc-21-108\method-optimization-report-of-particle-size-distribution.pdf

Assessor's Comments on Applicant's response to Deficiency #2:
In the current amendment, Lupin highlighted that they intentionally manufactured process/formula batches to study the impact of critical parameters on the dissolution testing. The applicant provided further explanation and evidence of the data, intentionally manufactured batches (PRS/2086/131B, PRS/2086/136, PRS/2086/137, PRS/2086/138, PRS/2086/131A, PRS/2086/132, PRS/2086/133, PRS/2086/134 and PRS/2086/135A) are not all showing discriminatory ability on IVRT method. However, the applicant has provided supportive evidence and explanation that the impact of the pH, viscosity, and PSD specification limits is capable to provide adequate discrimination to reject batches. As provided in the table by the applicant, batch # PRS/2086/131B fails in similarity factor (f2 = 44) as well as the pH specification limit (b) (4). Lupin noted in this case both IVRT and pH are displaying discriminatory ability. On the other hand, batch # PRS/2086/131A, has f2=60 but fails in pH specification. Although the IVRT is not discriminatory, the pH specification (b) (4) is not within the specification limits (b) (4) thus the pH discriminates and rejects the batch.

Furthermore, the formulation variable batches (batch # PRS/2086/136, PRS/2086/137, and PRS/2086/138) with higher PSD (d50) (b) (4) against proposed specification limit of (b) (4) displayed f2 similarity values below 50. The f2 values were below 50 due to the difference in d50. The applicant's submitted data and explanation in the current amendment suggest that PSD (d50) is the discriminatory critical attribute that impacts dissolution.

The applicant has provided reasonable explanation to address deficiency comment #2. The applicant's response is adequate.

Bioequivalence Deficiency #3

In your IVRT study, you reported rejected sets. You stated: "In two analytical runs of 12 units for each Test (Lot #H190068) and Reference (Lot #09634) were not in trend and variations were observed on % drug releases and these were investigated through the Analyst Check List for OOE i.e., DR/OOE/21/0005. The root cause is identified for low release, and which was not in trend. And this happened due to improper precautions and wrong vial filled while analysis". However, you did not provide raw data for all analytical runs including the rejected runs. Please submit the missing information. In addition, please provide the investigation report if applicable on the rejected runs.

Applicant's Response:
As requested by the Agency, we have provided raw data for all analytical runs (i.e., accepted and rejected runs) of Test Batches and Reference Batches (RLD Lots) along with Investigation Report in Vitro Release Test (IVRT) study.

Assessor's Comments on Applicant's response to Deficiency #3:
The applicant submitted the requested missing documents, including raw data for all analytical runs for test and reference as well the Investigation Report. Within the investigation report, the applicant clearly explained that during analysis the % drug release was stopped in some units and therefore release is not in increasing order. The human error due to not following the precautions and incorrect vial filling were the root cause for the incomplete drug release and % drug release fluctuations in multiple cell units. The sample units were repeated per the applicant's protocol as the stoppage during sample analysis did not provide sufficient analysis. The repeated analysis was found to be adequate in original BE assessment.

The applicant's response is adequate.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 216935

APPLICANT: Lupin Limited

DRUG PRODUCT: Prednisolone Acetate Ophthalmic Suspension USP, 1%

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

5 OUTCOME

COMPLETED ASSIGNMENT FOR 216935 ID: 49309

Reviewer: Smith, Taylor **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Prednisolone Acetate Ophthalmic Suspension USP,1%

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*		
49309	09/19/2022	BIO	ANDA Amendment [1]	1	1	Edit	Delete
49309	09/19/2022	Parallel	Minor Amendment (Original or Supplement) [1]	1	1	Edit	Delete
49309				Total:	2		

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	216935	
Drug Product Name	Prednisolone Acetate Ophthalmic Suspension USP	
Strength(s)	1%	
Applicant Name	Lupin Limited	
Applicant Address	Off Western Express Highway 3rd Floor, Kalpataru Inspire, Santacruz (East) Mumbai, Maharashtra 400055 India	
US Contact Name and US Mailing Address	Ms. Kalpana Vanam Senior Vice President, Regulatory Affairs Lupin Pharmaceuticals, Inc. 400 Campus Drive Somerset, New Jersey 08873 kalpanavanam@lupin.com	
US Contact Telephone Number	(b) (6) (Office) 443-562-6704	
US Contact Fax Number	N/A	
Original Submission Date(s)	04/11/2022	
Submission Date(s) of Amendment(s) Under Review	N/A	
Primary Reviewer	Taylor Smith, Ph.D.	
Secondary Reviewer	Svetlana Cherstniakova, Ph.D.	
Tertiary Reviewer	Wendy Cai, Ph.D.	
Study Number(s)	LBC-21-108	(b) (4)-DR/2021/MIR/0010/1.0
Study Type(s)	Drug Particle Size Distribution	In Vitro Release Test
Strength(s)	1%	1%
Clinical Site	N/A	
Clinical Site Address	N/A	
Analytical Site	Lupin Bioresearch Center In Vitro BE Lab	(b) (4)
Analytical Site Address	Lupin Bioresearch Center Invitro BE Lab 46A/47A, Lupin Research Park, Nande Village, Taluka Mulshi Pune – 412 115, Maharashtra, India Ph.: +91-20-66219200	

	Lupin Bioresearch Center Survey No. 146/2/1B, Sai Trinity, Wing - A, Pashan Pune – 411 021, Maharashtra, India Ph.: +91-20-66219200		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)[1]	**Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent)[1]	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☒ Inadequate ☐ N/A		
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	***Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)*** ☒ Recommended/Latest Revision Date: _05/2019; __ RLD Number: __ NDA 017011 _____ ☐ 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, 3, 4	**Formulation Q1/Q2**	**1%**	☒ Adequate ☐Inadequate
1, 3, 4	**Particle Size**	**1%**	☐ Adequate ☒Inadequate

[1] Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

1,3,4	**In Vitro Release Test**	**1%**	**☐ Adequate ☒Inadequate**
1,3,4	**Waiver/Deem Bioequivalent**	**1%**	**☐ Adequate ☒Inadequate**

1 EXECUTIVE SUMMARY

Lupin Limited has requested a waiver of in vivo bioequivalence (BE) testing for its test product, Prednisolone Acetate Ophthalmic Suspension USP, 1% under Section 21 CFR § 320.24(b)(6). The reference listed drug (RLD) and reference standard (RS) is Pred Forte® (prednisolone acetate) Ophthalmic Suspension,1% manufactured by Allergan Pharmaceutical approved under NDA 017011, prior to 01/01/1982[5].

The current draft Product Specific Guidance (PSG) for Prednisolone Acetate Ophthalmic Suspension recommends two options: 1) In vitro option and 2) In vivo option. The applicant selected in vitro option to establish BE. The Agency's current recommendations for in vitro option include: 1) the test product should be qualitatively (Q1) and quantitatively (Q2) the same as the RLD product for all inactive ingredients; 2) acceptable comparative physicochemical characterization of the of the test and reference standard (RS) products (including pH, specific gravity, osmolality, buffer capacity, surface tension, viscosity, soluble fraction, and drug particle size distribution); and 3) acceptable comparative in vitro drug release test (IVRT) of prednisolone acetate.

Based on the information submitted, the applicant's test product is Q1 and Q2 the same as the approved RLD product. Additionally, the three batches of the test product [Batch #H190066, #H190067 and #H190068] and reference product [Lot #08632, Lot #09116, Lot #09634] were used for in vitro physicochemical characterization studies. The results of in vitro comparative pH, specific gravity, osmolality, buffer capacity, surface tension, and viscosity provided by the applicant in the current application are comparable between the test and reference products.

The applicant provided results of particle size distribution (PSD) study as the study was performed on three batches each of test and reference products. The population bioequivalence (PBE) analysis based on D50 and SPAN [i.e., (D90-D10)/D50)] met the BE acceptance criteria.

Method: PBE for PSD Study (N=30) Least Squares Geometric Means, Ratio of Means, and 95% Upper Confidence Bound								
Parameter	Geometric Mean			Standard Deviation		95% upper confidence bound	Method Used	Outcome
	Test	Reference	Ratio	Sigma T	Sigma R			
D_{50}							(b) (4)	Pass
span								Pass

However, the in vitro PSD study is inadequate related to a missing method development report to support the obtained results.

There is no USP-method or FDA recommended drug release method for this product. The applicant conducted comparative IVRT of prednisone acetate from the test and RLD formulations using the method shown below and three different batches of test and

reference products. The f2 values calculated by the BE assessor are above 50, demonstrating comparable in vitro drug release between the test and reference products.

Apparatus	USP apparatus IV
Medium	Phosphate Buffer, pH 5.5
Medium Volume	150 mL
Medium temperature	35°C ± 0.5°C
Flow	8.0 ml/min
Flow through cell	22.6 mm
Sampling Time Points	5, 10, 15, 20, 30, 60, 90 and 120 minutes
Sample Withdrawal Volume	5.0 ml

The applicant noted rejected runs per the comparative in vitro drug release study report. The results of Test (H190068) and Reference (09634) were not in trend and variations were observed. The applicant states that, *the root cause is identified for low release and which was not in trend. And this happens due to improper precautions and wrong vial filled while analysis*. The applicant did not provide raw data and the investigation report for the rejected runs. The applicant's IVRT results are inadequate.

The in vitro drug release testing is being assessed separately by the Office of New Drug Products (ONDP) for establishing the quality control method and specifications for batch release. The evaluation on the method appropriateness and discriminating ability against the critical process variability as well as the critical quality attributes in the manufacturing of the product is pending[2].

OSIS Status "Complete"

Decline to Conduct an On-Site Inspection Memos checked in and OSIS task is complete.

Per GDRP, OSIS previously inspected Lupin Bioresearch Center[3] and (b) (4) . A Remote Record Review for the sites, Lupin Bioresearch Center was conducted in September 2021 and (b) (4). OSIS concluded that data from the reviewed studies were reliable. OSIS determined that an inspection is not warranted at this time for the aforementioned sites. 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.

[2] GDRP. ANDA 216935. Biopharmaceutics Quality Review.
https://panorama.fda.gov/task/view?ID=625571f700d3e6d16ff69d79aed8f582
[3] https://panorama.fda.gov/task/view?ID=625747bd004ba4082a4968f8d78dca81
(b) (4)

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Prednisolone Acetate Ophthalmic Suspension USP, 1%
Reference Standard (RS) and Strength(s)	Pred Forte® (Prednisolone Acetate) Ophthalmic Suspension/drops, 1 %
RS Holder; NDA/ANDA Number; Approval Date[5]	Allergan Pharmaceutical; NDA 017011; approved prior to 01/01/1982
Reference Listed Drug (RLD) and Strength(s)	Pred Forte® (Prednisolone Acetate) Ophthalmic Suspension/drops, 1 %
RLD Holder; NDA/ANDA Number; Approval Date[5]	Allergan Pharmaceutical; NDA 017011; approved prior to 01/01/1982

3.2 PK/PD Information[6,7]

Most recent RLD label (provide embedded document)	 Id No NG/G tube study is needed. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/017011s050lbl.pdf
Indication	PRED FORTE® is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
Boxed warning	NA
Bioavailability	Prednisolone is absorbed through the aqueous humor, with only minimal systemic absorption occurring.
Food Effect	NA
Tmax	NA
Metabolism	Ophthalmic preparations distribute into the local tissues and are metabolized locally.
Excretion	NA
Half-life	NA
Maximum Daily Dose	1 or 2 drops into affected eye(s) every hour while awake, and every 2 hours at night

[5] Per Orange Book, NDA 017011; https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=017011#19820
[6] Drugs@FDA. Search NDA 017011; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/017011s050lbl.pdf
[7] Clinical Pharmacology, Prenisolone, https://www.clinicalkey.com/pharmacology/monograph/504?sec=monindi&aprid=31603

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	PSG **PSG recommended date April 2104; Revised June 2016, May 2019**[8]	
Summary of OGD or DB History	Approved ANDAs:	None
	Pending ANDAs:	216935 (current)
	Controls:	Control #: 9046454, 10245860, 13677819, 15384612, 18758991, 22236982, 25465938, 00587, 12676, 37229, 04150
	Protocols:	N/A
	Pending Citizen Petitions and other legal and regulatory issues: If yes, please comment.	☐ Yes ☒ No

Assessor's Note

Previous Controlled Correspondences (CC)

CC 9046454[9]:

On July 11, 2016, the applicant submitted request for qualitative/quantitative (Q1/Q2) evaluation for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%.

In response, the Agency noted that the proposed formulations are not Q1-Q2 to the RLD formulation with respect to one or more inactive ingredients.

CC 10245860[10]:

CC dated September 16, 2016 references CC# 9046454 and the Agency response. CC# 10245860 submitted request for Q1/Q2 for the proposed revised formulation for test product, Prednisolone Acetate Ophthalmic Suspension, USP 1%.

In response, the Agency noted that the proposed formulations are not Q1-Q2 to the RLD formulation with respect to one or more inactive ingredients.

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[8] Product-Specific Guidance for Generic Drug Development. https://www.accessdata.fda.gov/drugsatfda_docs/psg/Prednisolone%20acetate%20Ophthalmic%20suspension%20RLD%20017011%20PSG%20Page%20RV%20May%202019.pdf

[9] https://panorama.fda.gov/project/view?ID=578407a50018d8a7cf3afaaabfdd9021

[10] https://panorama.fda.gov/project/view?ID=57dff1c10217d46f2e7f188c7afc112d

CC 13677819[11]:
On March 10,2017, the applicant submitted request for Q1/Q2 evaluation for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%.
In response, the Agency noted that the proposed formulations are not Q1-Q2 to the RLD formulation with respect to one or more inactive ingredients.

CC 15384612[12]:
On May 26,2017, the applicant submitted request for Q1/Q2 evaluation for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%.
In response, the Agency noted that the proposed formulations are not Q1-Q2 to the RLD formulation with respect to one or more inactive ingredients.

CC 18758991[13]:
On November 2,2017, the applicant submitted request for Q1/Q2 evaluation for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%.
In response, the Agency noted that the proposed formulations are not Q1-Q2 to the RLD formulation with respect to one or more inactive ingredients.

CC 22236982[14]:
On April 6, 2018, the applicant submitted request for Q1/Q2 evaluation for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%.
In response, the Agency noted that the proposed formulations are not Q1-Q2 to the RLD formulation with respect to one or more inactive ingredients.

CC 25465938[15]:
On August 23, 2018, the applicant submitted request for Q1/Q2 evaluation for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%.
In response, the Agency noted that the proposed formulations are not Q1-Q2 to the RLD formulation with respect to one or more inactive ingredients.

CC 00587[16]:
On October 30, 2018, the applicant submitted request for Q1/Q2 evaluation for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%.
In response, the Agency noted on June 4, 2021 that the proposed formulations are not Q1-Q2 to the RLD formulation with respect to one or more inactive ingredients.

CC 04150[17]:

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[11] https://panorama.fda.gov/project/view?ID=58c6acec02e5cdb59207e90e0448c63b
[12] https://panorama.fda.gov/project/view?ID=59300418006042abde28491f4524c422
[13] GDRP. https://panorama.fda.gov/project/view?ID=5a006d3e0074b9899f92c7a01f707d5d
[14] https://panorama.fda.gov/project/view?ID=5acce7b400219bcca2300c91ab26548b
[15] GDRP. https://panorama.fda.gov/project/view?ID=5b840020006ba935f2eb3883b5d47412
[16] GDRP. https://panorama.fda.gov/project/view?ID=5bd8c46c003133d11d7495bdd971c9c7
[17] GDRP. https://panorama.fda.gov/project/view?ID=5d154333002d4be709f13b8870f7cb51

On June 27, 2019, the applicant submitted request to confirm if it is acceptable to conduct in vitro studies only on the 5 mL fill size bottle of the test and reference products for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%.
In response, the Agency noted on August 13, 2019, that the applicant's bioequivalence studies on test and RS product appears reasonable.

CC 12676[18]:
On June 26, 2020, the applicant submitted request for confirmation on the number of batches for the proposed formulation, Prednisolone Acetate Ophthalmic Suspension, USP 1%. The applicant is developing a generic formulation of Pred Forte (prednisolone acetate ophthalmic suspension) 1%. Lupin intends to manufacture three exhibit batches.
In response, the Agency noted on August 19, 2020 that the proposed approach for exhibit batch manufacturing and stability testing is acceptable.

CC 37229[19]:
On June 22, 2021, the applicant submitted request for Q1/Q2 evaluation for the proposed formulation for Prednisolone Acetate Ophthalmic Suspension, USP 1%. In response, the Agency noted on August 4, 2021 that the proposed formulations are Q1/Q2 same to the RLD formulation.

[18] https://panorama.fda.gov/project/view?ID=5ef94c5600049c81a91ecf30af09a97a
[19] Nexus. https://cdernexus.fda.gov/suite/sites/controlled-correspondence/page/search/record/lUBIZ8AFspSx36FNxwhBVkJHPTqDy48HOG_jHiHbnOIYh9dV8pn9S-FNB-AtfqmJj-dmfh8FujhIfsTeLxyrvo0HX5B4ybovSUU6Y4ZlyKNbJghzU7b/view/summary

4 APPENDIX

4.1 Formulation Data

4.1.1 Test Formulation

Composition of Prednisolone Acetate Ophthalmic Suspension USP 1%

Ingredients [Grade]	1%			Category	Reference to Standards
	Unit Quantity (mg/mL)	%w/v	%w/v		
Prednisolone acetate* $ (b) (4)	10.000	1.000	1.000	Active Ingredient	USP
Benzalkonium Chloride (b) (4)^	(b) (4)			(b) (4)	NF
Edetate disodium (b) (4)					USP
Polysorbate 80					NF
Sodium Bisulfite#					IH
Hypromellose 2906 (b) (4)					USP
Boric Acid					NF
Sodium Citrate (b) (4)					USP
Sodium Chloride					USP
Water for Injection¥					USP
(b) (4)					NF

(b) (4)

(b) (4)

(b) (4)

Assessor's Note: Per CC37229 review[21], RLD has edetate disodium (b) (4)

4.1.3 Comparative Compositions of the Test and RLD Products

Ingredients Component	Test Formulation (mg/mL)	RLD Formulation (mg/mL)	Difference ([T-R]/R *100)
Prednisolone acetate	(b) (4)		
Benzalkonium Chloride			

[20] EDR. NDA017011. Module 3.2.P.3 Batch Formula. \\CDSESUB1\evsprod\nda017011\0027\m3\32-body-data\32p-drug-prod\pred-forte-ophthalmic-suspension\32p3-manuf\batch-formula.pdf

[21] Nexus. https://cdernexus.fda.gov/suite/sites/controlled-correspondence/page/search/record/lUBIZ8AFspSx36FNxwhBVkJHPTqDy48HOG_iHiHbnOlYh9dV8pn9S-FNB-AtfqmJi-dmfh8FujhIfsTeLxyrvo0HX5B4ybovSUU6Y4ZlyKNbJghzU7b/view/summary

Edetate disodium (b) (4)	(b) (4)
Boric Acid	
Hypromellose (b) (4) (b) (4)	
Polysorbate 80	
Sodium Bisulfite	
Sodium Citrate (b) (4)	
Sodium Chloride	

Comments on Formulation:
The composition of test product in the submission is the same as that deemed Q1/Q2 same in CC 37229. The test drug product, Prednisolone Acetate Ophthalmic Suspension USP, 1% contains the same amounts of active ingredients as that of the RLD product, Pred Forte® (prednisolone acetate) Ophthalmic Suspension, 1 % (NDA 017011). The route of administration, dosage form, and strength of the test product are the same as those of the RLD product. (b) (4) . The test product formulation is Q1/Q2 the same as the RLD and is adequate.

4.2 Product Information

Product	Test			Reference		
Treatment ID	T			R		
Product Name	Prednisolone acetate ophthalmic suspension, USP 1%			PRED FORTE® (Prednisolone acetate ophthalmic suspension, USP) 1% sterile		
Manufacturer / Distributer	Lupin Limited, Plot No. 2, SEZ Phase-II, Misc Zone, Apparel Park, District Dhar, Pithampur, Indore, Madhya Pradesh 454775, India.			Allergan USA, Inc. Madison, NJ 07940.		
Marketed By	Not Applicable			Not Applicable		
Batch/Lot No.	H190066, H190067 and H190068			08632, 09116 and 09634		
Manufacture Date	JUN 2021, JUN 2021 and JUL 2021			Not Available		
Expiration Date	MAY 2023, MAY 2023 and JUN 2023			APR 2022, JUL 2022 and SEP 2022		
Strength	1%			1%		
Dosage Form	Suspension			Suspension		
Bio-batch Size	(b) (4) bottles			Not Applicable		
Production Batch Size	Not Applicable			Not Applicable		
Potency	Lot No. H190066	Each mL of ophthalmic suspension	(b) (4)	Lot No. 08632	Each mL of ophthalmic suspension	(b) (4)

Product	Test	Reference
	contains Prednisolone acetate USP Label Claim: 1% Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim:10 mg (b) (4)	contains Prednisolone acetate USP Label Claim: 1% Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim:10 mg (b) (4)
	Lot No. H190067: Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim: 1% Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim:10 mg Lot No. H190068: Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim: 1% Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim:10 mg (b) (4)	Lot No. 09116: Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim: 1% Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim:10 mg Lot No. 09634: Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim: 1% Each mL of ophthalmic suspension contains Prednisolone acetate USP Label Claim:10 mg (b) (4)
Content Uniformity (mean, % CV)	Not Applicable	Not Applicable
Dose Administered	Not Applicable	Not Applicable
Route of Administration	Ophthalmic	Ophthalmic

4.3 In vitro Physicochemical Characterization

4.3.1 Study Information

Study Number	LBC-21-108			
Study Title	*In-Vitro* comparative study of Physicochemical characterization, Soluble fraction and Particle size distribution of Prednisolone acetate ophthalmic suspension, USP 1% manufactured by Lupin Limited, India with PRED FORTE® (Prednisolone acetate ophthalmic suspension, USP) 1% sterile Distributed by Allergan USA, Inc. Madison, NJ 07940.			
Study Type	☐ In Vivo BE	☒ In Vitro BE	☐ Permeability	☐ Other (Specify)
Submission Location:				
Study Report	m5.3.1.4			
Validation Report	m5.3.1.4			
Bioanalytical Report	m5.3.1.4			
Clinical Site (Name, Address, Phone #, Fax#)	Not Applicable			
Principal Clinical Investigator (Name, Email)	Not Applicable			
Analytical Site (Name, Address, Phone #, Fax#)	Lupin Bioresearch Center Invitro BE Lab 46A/47A, Lupin Research Park, Nande Village, Taluka Mulshi Pune – 412 115, Maharashtra, India Ph.: +91-20-66219200 Lupin Bioresearch Center Survey No. 146/2/1B, Sai Trinity, Wing - A, Pashan Pune – 411 021, Maharashtra, India Ph.: +91-20-66219200			
Principal /Analytical Investigator (Name, Email)	Analytical investigator: Mr. Dipak Raut, M.Sc. Email: dipakraut@lupin.com			
Study Dates	11/26/2021-12/15/2021			
Sample Storage: **a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **b) Temperature Range**	Not Applicable			
Long Term Storage Stability (LTSS) Coverage (no. days @ temp°C)	Not Applicable			
LTSS Data Location	Not Applicable			

4.3.2 pH

The pH of the test and RLD product is comparable. The pH specification of the test formulation is within the RLD pH acceptance range, 5.0 to 6.0.

	Test[22]			RLD[23]		
	H190066	**H190067**	**H190068**	**Lot 08632**	**Lot 09116**	**Lot 09634**
pH	(b) (4)					
Acceptance Criterion	5.0 – 6.0			5.0 – 6.0		

4.3.3 Osmolality

Per the PSG, the applicant conducted osmolality testing. The osmolality results[24] are shown below.

(b) (4)

The osmolality results above show that osmolality for both the test and reference products are within the acceptance criteria.

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[22] EDR. ANDA 216935. Module 3.2.P.5.1 Specifications. \\CDSESUB1\evsprod\anda216935\0002\m3\32-body-data\32p-drug-prod\predopsusp-1-suspnsionoph-lupinltd\32p5-contr-drug-prod\32p51-spec\fps-1-fpf2-832.pdf

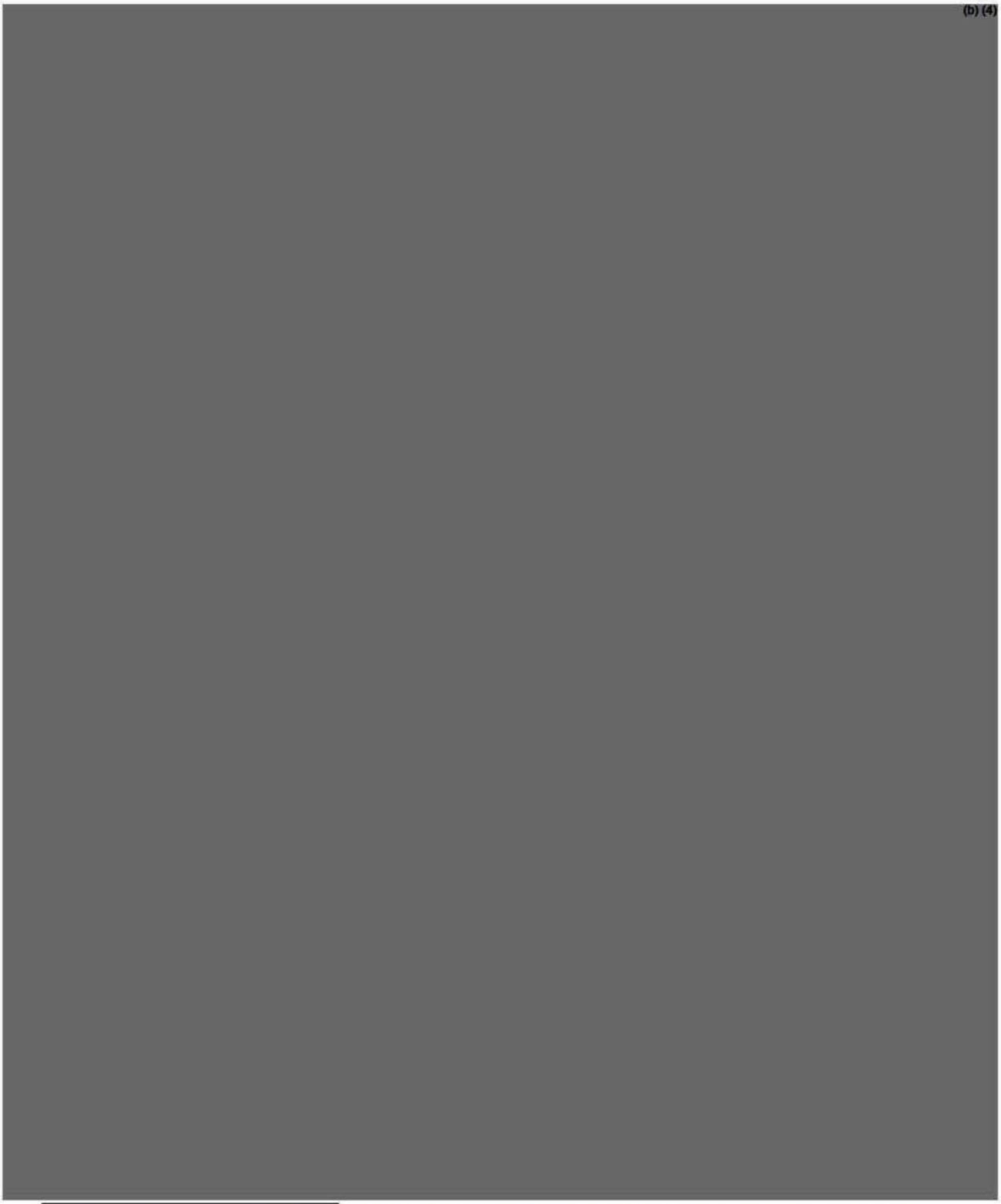
[23] EDR. Module 3.2.P.5.1 Specifications. \\CDSESUB1\evsprod\nda017011\0003\m3\32-body-data\32p-drug-prod\pred-forte-ophthalmic-suspension\32p5-contr-drug-prod\32p51-spec\specifications.pdf

[24] EDR. Module 5.3 Clinical Study Reports. Individual Sample Measurement Data. \\CDSESUB1\evsprod\anda216935\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\lbc-21-108\pe-iv-13-1-5-individual-sample-measurement-data.pdf

4.5 In Vitro Drug Release Test (IVRT)

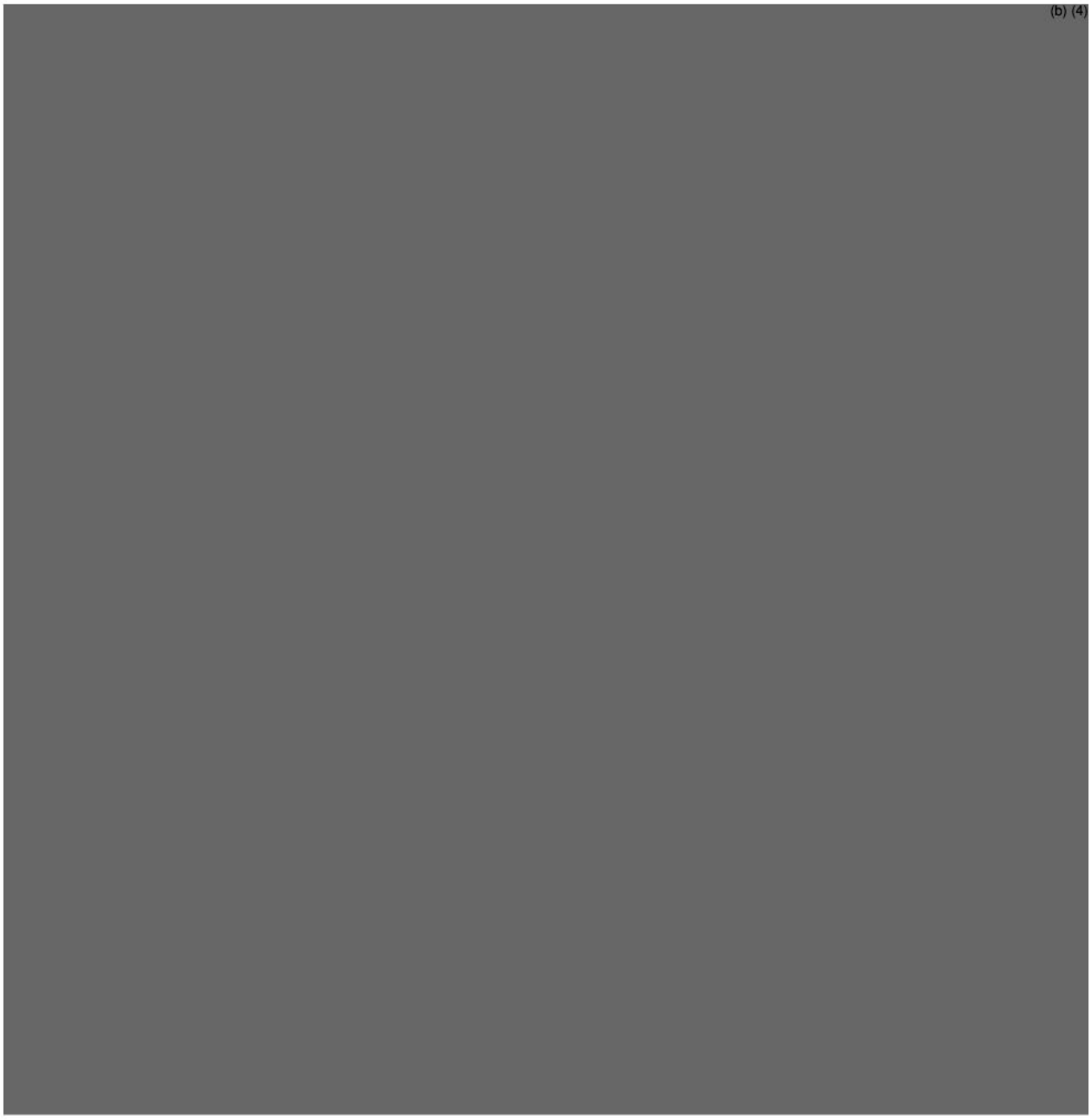
4.5.1 Study Information

Study Number	(b) (4)DR/2021/MIR/0010/1.0			
Study Title	*Comparative In vitro* Drug release study to evaluate the Dissolution profile of Prednisolone Acetate in Prednisolone Acetate Ophthalmic Suspension, USP 1 % of Lupin Limited, India, with PRED FORTE® (Prednisolone Acetate Ophthalmic Suspension, USP) 1 % distributed by Allergan ™, Madison, NJ 07940, USA.			
Study Type	☐ In Vivo BE	☒ In Vitro BE	☐ Permeability	☐ Other (Specify)
Submission Location: **Study Report**	m5.3.1.4			
Validation Report	m5.3.1.4			
Bioanalytical Report	m5.3.1.4			
Clinical Site (Name, Address, Phone #, Fax#)	Not Applicable			
Principal Clinical Investigator (Name, Email)	Not Applicable			
Analytical Site (Name, Address, Phone #, Fax#)	(b) (4)			
Principal /Analytical Investigator (Name, Email)				
Study Dates				



[28] \\CDSESUB1\evsprod\anda216935\0004\m3\32-body-data\32p-drug-prod\predopsusp-1-suspnsionoph-lupinltd\32p2-pharm-dev\analytcl-mthd-devlp-report-drug-release.pdf

[29] ANDA 216938. Biopharmaceutics IR. https://panorama.fda.gov/internal/document/preview?versionID=62bb40c7002b439b705d27ddb91ec922&ID=62bb3b3c0029c4a78497d72c8d052a39



In vitro drug release test method development:

To demonstrate discriminatory ability, the applicant evaluated the IVRT method using USP Type-IV apparatus and the following dissolution parameters listed below:

Dissolution Parameters:

Medium	: Phosphate buffer pH 5.5
Media volume	: 150-mL
Temperature	: 35°C ± 0.5°C
Apparatus	: USP Type-IV (Closed Loop)
Flow	: 8.0 mL/ minute
Time	: 5, 10, 15, 20, 30, 60, 90 and 120 minutes
Withdrawn Volume	: 5-mL
Replenish Volume	: 5-mL
Flow through cell	: 22.6mm

Sample Details:

Details of samples (API and Finished Product) used for method development are as follows:

Name of the substance	Batch No.	Source
Drug substance	ZPRACY17004S-11	(b) (4) [redacted]
Placebo for Prednisolone Acetate	P2441C14	
Sample	H190066, RS/2086/131A, PRS/2086/131B, PRS/2086/132 PRS/2086/133, PRS/2086/134, PRS/2086/135, PRS/2086/136, PRS/2086/137, PRS/2086/138	
RLD	09116, 08632	Allergan USA Inc. Madison, NJ 07940

Selection of Dissolution Media:

In ideal situation the dissolution medium should be in line with eye physiological conditions, and lacrimal fluid composition having pH 7.4. (b) (4) [redacted] As the drug product pH is in the range of 5.0 - 6.0 and drug is stable in this pH range. Therefore, pH 5.5 phosphate buffer selected as dissolution medium is acceptable.

Selection of flow rate:

Dissolution has been performed to optimize the flow rate with flow rate (b) (4) [redacted]. The applicant's selection of 8.0 mL/minute flow rate for further study is acceptable.

Selection of dissolution medium volume:

Dissolution has been performed with media volume (b) (4) [redacted]

[redacted] (b) (4)

. The applicant's selection of 150 mL media volume is acceptable.

Based on the data submitted showing drug release profiles in the selected IVRT method, the final selection of parameters was found acceptable by the assessor.

Evaluation of the discriminating capability of the method:

The applicant compared the drug release profiles for the following batches (i.e., exhibit batch, critical formulation variable (CFVs) batches, critical process parameters (CPPs) batches and CFVs and CPPs batch) to determine the discriminatory ability of the method.

[redacted] (b) (4)

F2 values comparing different batches are listed below:

Time (Min)	% Drug release in pH 5.5 Phosphate Buffer					
	H190066	PRS/2086/131A	PRS/2086/131B	PRS/2086/132	PRS/2086/134	PRS/2086/133
5	28	30	23	28	26	21
10	50	49	43	49	49	40
15	65	60	53	59	60	57
20	75	67	58	65	68	70
30	85	74	66	73	77	82
60	91	84	75	84	87	89
90	92	88	80	89	91	91
120	93	92	84	92	92	92
f2 against H190066		**60**	**44**	**58**	**64**	**59**

Time (Min)	% Drug release in pH 5.5 Phosphate Buffer					
	H190066	PRS/2086/135A	PRS/2086/135B	PRS/2086/136	PRS/2086/137	PRS/2086/138
5	28	17	29	5	17	12
10	50	40	51	20	33	27
15	65	56	63	38	47	40
20	75	65	70	55	56	51
30	85	75	78	75	66	63
60	91	85	88	92	76	78
90	92	89	91	96	81	86
120	93	92	92	97	85	90
f2 against H190066		**51**	**70**	**34**	**40**	**37**

- The applicant provided details including pH, viscosity, and PSD on batches with process variations. Although, some process/formula variation batches are above 50, the f2 values for batches: PRS/2086/131B, PRS/2086/136, PRS/2086/137 and PRS/2086/138 were below 50 and therefore were not comparable to batch no. H190066. These differences are reflected as relative change in f2 values of exhibit batch against process/formula variation batches. The method successfully discriminated variabilities on process/formula among different test batches, the f2 similarity values were reduced from 70 to around 34 due to process/formula variability.
- However, the process formula variable batches with increasing particle size may not always have f2 <50 as the results of batch 135A (f2 = 51). Therefore, the applicant will be asked to provide explanation on why they deemed the method discriminating based on the results (f2>50) of batches PRS/2086/131A, PRS/2086/132, PRS/2086/133, PRS/2086/134 PRS/2086/135A and PRS/2086/135B.

The applicant conducted a comparative in vitro drug release study to evaluate the dissolution profile of prednisolone acetate in Prednisolone Acetate Ophthalmic Suspension, USP 1%. The dissolution testing parameters[30] are shown below.

Dissolution Conditions	**Apparatus:**	USP Type-IV (Closed Loop)
	Speed of Rotation:	N/A
	Flow	8.0 mL/minute

[30] EDR. ANDA 216935. Study Protocol. \\CDSESUB1\evsprod\anda216935\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met [redacted]dr-2021-mir-0010\study-protocol.pdf

	Medium:	Phosphate buffer pH 5.5
	Volume:	150 ml
	Temperature:	37°C ± 0.5°C
	Time:	5, 1 0, 1 5, 20, 3 0, 60, 90 and 120 minutes
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site		(b) (4)

The analytical method selected in the IVRT study is summarized as below.

Dissolution Media Preparation: (Phosphate Buffer pH 5.5 Preparation)
Dissolve 1 .4 g of Disodium hydrogen phosphate anhydrous in 1000-mL of water. Adjust to pH 5.5 ± 0.05 with orthophosphoric acid solution. Sonicate for 10 minutes.

(b) (4)

Procedure:

4.5.3 Method Validation for In Vitro Release Test

The following parameters were validated for the dissolution of prednisolone acetate in Prednisolone Acetate Ophthalmic Suspension USP 1 % in report no. (b) (4) DR/2021/MVR/0204/1.0[31].

[31] EDR. ANDA 216935. Method Validation Report. \\CDSESUB1\evsprod\anda216935\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met (b) (4) dr-2021-mir-0010\method-validation-report-disso.pdf

(b) (4)

System Precision Results

Injection #	Prednisolone Acetate
	Peak area
1	(b) (4)
2	
3	
4	
5	
6	
Mean of 6 replicates	419214
%RSD for 6 replicates	0.2

Acceptance criteria: The % RSD of Peak area for 6 replicate injections of Prednisolone Acetate peak from Standard Solution-2 should be not more than 2.0.

Precision Results

Time interval (in minutes)	%Drug Release						Mean	% RSD
	Cell-1	Cell-2	Cell-3	Cell-4	Cell-5	Cell-6		
5	(b) (4)						25	3.9
10							51	5.9
15							71	6.9
20							84	4.9
30							94	3.0
60							99	2.1
90							100	2.1
120							100	2.0

Acceptance criteria: % RSD of drug release of six test unit should not be more than 5.0% for last time point.

Intermediate Precision Results

Time interval (in minutes)	%Drug Release						Mean	% RSD
	Cell-1	Cell-2	Cell-3	Cell-4	Cell-5	Cell-6		
5	(b) (4)						26	2.1
10							52	0.8
15							70	0.9
20							80	0.9
30							88	0.9
60							96	0.9
90							98	0.8
120							98	1.2

Cumulative %Drug Release Results

Name	Time interval (in 120 minutes)	
	Method precision	Intermediate precision
Cell-1	(b) (4)	
Cell-2		
Cell-3		
Cell-4		
Cell-5		
Cell-6		
Mean	99	
%RSD	1.9	

Acceptance criteria: % RSD of drug release of six test unit should not be more than 5.0% for last time point.

Linearity Results

Linearity Levels (%)	Prednisolone Acetate	
	Concentration in ppm	Peak Area
10% of Q	(b) (4)	
50		
80		
100		
120		
150		
Correlation Coefficient		
Intercept		
Slope	64912.9407	
%Y-intercept	0.3	
Residual sum of squares	35645952	

Accuracy Results

Sample #	Spike Level	Added (in ppm)	Found (in ppm)	% Recovery	Mean % Recovery	% RSD
1	50% (ofQ value)	[redacted] (b) (4)			96.8	2.7
2						
3						
1	100%				103.3	0.1
2						
3						
1	150%				99.6	0.2
2						
3						

Range

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity. Based on method precision, linearity, and accuracy the range of method for linearity is from 0.3875 ppm to 9.6883 ppm.

Sample Solution Stability Results

Table 17 Sample Solution stability Results

Time interval (in hours)	Peak area	%Difference
Initial	429638	NA
16.6	425898	0.9
25.6	416994	2.9
34.6	399421	7.0
43.6	375270	12.7

Reference: LNB Number:7844, page No.:055.

Table 18 Standard Solution stability Results

Time interval (in hours)	Peak area	%Difference
Initial	426543	NA
16.6	426626	0.0
25.6	427005	-0.1
34.6	426433	0.0
43.6	424536	0.5
53.4	422475	1.0
77.1	415795	2.5
101.4	407102	4.6

Per the acceptance criteria, prednisolone acetate peak area %drug release should not differ by ± 5% from initial time interval for standard and sample solution.

The applicant noted that the standard solution is stable up to 101 hours and the sample solution is stable up to 26 hours.

Robustness
Robustness was evaluated by injecting blank and standard solution at flow rate variation, column oven temperature change, wavelength change, mobile phase variation, variation of dissolution media pH and variation in dissolution temperature. The results of robustness for the analytical method and dissolution method were found within the acceptance criteria and demonstrated robustness.

Filter Study
The area difference of filtered solution should not differ ± 5.0% from unfiltered solution. The filter study results demonstrated that the Filter [redacted] (b) (4)) is suitable for %drug release using USP-Type-IV apparatus for prednisolone acetate in Prednisolone Acetate Ophthalmic Suspension USP 1 .0%.

Assessor Comments:
The method was validated for its system suitability, specificity, precision (system precision, method precision, intermediate precision), linearity, accuracy, range, solution stability, robustness, and filter interference. The assessor checked the method validation report and verified that all the method validation parameters met the acceptance criteria. The results of applicant's method validation and analytical method validation are acceptable.

4.5.4 In Vitro Drug Release Results

Three different batches of test and RLD products using 12 samples at different time interval at each batch were tested, and the obtained results of test product were compared with the corresponding results of RLD.

Dissolution Parameters:

Medium	: Phosphate buffer pH 5.5
Media volume	: 150-mL
Temperature	: 35°C ± 0.5°C
Apparatus	: USP Type-IV (Closed Loop)
Flow	: 8.0 mL/ minute
Time	: 5, 10, 15, 20, 30, 60, 90 and 120 minutes
Withdrawn Volume	: 5-mL
Replenish Volume	: 5-mL
Flow through cell	: 22.6mm

% Drug Release for Test Product

Product	Lot No.	% Drug Release												Mean % Drug Release	% RSD
		Time (In minutes)	Sample Unit No.												
			1	2	3	4	5	6	7	8	9	10	11	12	
Test	H190066	5 min	[redacted] (b) (4)												28	14.9
		10 min													50	19.9
		15 min													65	16.0
		20 min													75	9.9
		30 min													85	8.3
		60 min													91	3.8
		90 min													92	3.5
		120 min													93	3.4
	H190067	5 min													26	6.4
		10 min													54	9.6

		15 min	[redacted] (b) (4)	72	7.6
		20 min		80	5.9
		30 min		87	4.2
		60 min		93	3.6
		90 min		94	3.2
		120 min		93	2.9
	H190068	5 min		25	6.2
		10 min		50	5.0
		15 min		65	6.9
		20 min		73	8.2
		30 min		80	7.3
		60 min		85	4.8
		90 min		86	3.9
		120 min		86	3.6

% Drug Release for Reference Product

Product	Lot No.	% Drug Release												Mean % Drug Release	%RSD
		Time (min)	Sample Unit No.												
			1	2	3	4	5	6	7	8	9	10	11	12	
Reference	08632	5 min	[redacted] (b) (4)												26	12.6
		10 min													51	6.8
		15 min													68	5.2
		20 min													76	6.1
		30 min													85	5.9
		60 min													92	4.4
		90 min													93	3.6
		120 min													94	5.0
	09116	5 min													24	10.5
		10 min													50	6.8
		15 min													65	8.4
		20 min													74	8.0

		30 min	(b) (4)	85	7.0
		60 min		93	5.9
		90 min		96	3.4
		120 min		96	2.5
	09634	5 min		26	14.3
		10 min		50	8.7
		15 min		63	9.7
		20 min		71	9.9
		30 min		80	9.2
		60 min		88	5.4
		90 min		90	4.0
		120 min		90	3.5

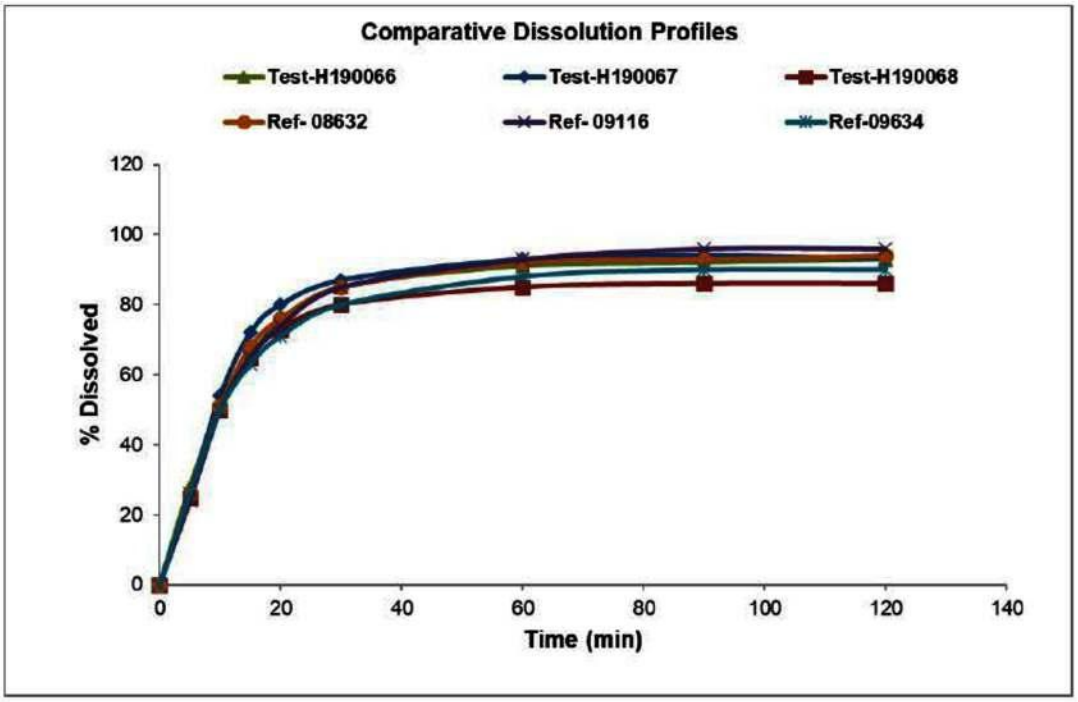
The applicant noted within comparative in vitro drug release study report rejected sets. In two analytical runs of 12 units for each Test (H190068) and Reference (09634) were not in trend and variations were observed. Details of rejected sample sets are shown in the table below.

Sequence Name	Experiment	Reason	Comment
PRED_OS_DISSO_ RLD_20220111_A	Drug release test for B.No. 09634 (6 Units)	(b) (4)	
PRED_OS_DISSO_ TEST_20220111	Drug release test for B.No. H190068 (6 Units)		
PRED_OS_DISSO_ RLD_20220111_A	Drug release test for B.No. 09634 (6 Units)		
PRED_OS_DISSO_ TEST_20220111	Drug release test for B.No. H190068 (6 Units)		

Assessor's Comments:

- In regard to the rejected sets, the applicant states in the comparative in vitro release study report that, *the root cause is identified for low release and which was not in trend. And this was happened due to improper precautions and wrong vial filled while analysis.*
- The applicant failed to provide raw data as well as rejected runs for test and reference batches for in vitro release testing submitted. The applicant will be asked to submit the missing raw data information along with an investigation report regarding the rejected runs and higher variations within in vitro release testing.

4.5.5 In Vitro Drug Release Profiles



4.5.6 F2 Metric

F2 metric calculated?	☒ Yes ☐ No

F2 Metric Test vs Reference

Test Product	Reference Product	Medium	F2 metric for Test vs RLD
Lot No. H190066	Lot No. 08632	Phosphate buffer pH 5.5	86.40
	Lot No. 09116		85.41
	Lot No. 09634		75.80
Lot No. H190067	Lot No. 08632		76.76
	Lot No. 09116		67.94
	Lot No. 09634		60.79
Lot No. H190068	Lot No. 08632		71.02
	Lot No. 09116		71.35
	Lot No. 09634		86.18

F2 Metric Test vs Test

Product(s)	Medium	F2 metric for Test vs RLD
Lot No. H190066 v Lot No. H190067	Phosphate buffer pH 5.5	69.03
Lot No. H190066 v Lot No. H190068		73.42

Comments on In Vitro Drug Release Testing: Inadequate

- The dissolution testing will be reviewed separately by the Division of Biopharmaceutics. The biopharmaceutics assessment team issued an IR dated 06/28/2022[29] requesting adequate method development report. The applicant's response was submitted on 07/28/2022 and was evaluated in the current assessment.
- There is no USP method for Prednisolone Acetate Ophthalmic Suspension. At the time of this review, the dissolution method and specifications for this product has not yet been posted on the FDA dissolution database[32].
- The applicant has provided comparative dissolution testing on three batches of the test product comparing to three batches of reference product. The f2-similarity factor was evaluated between the test and reference product. The f2 values comparing test and reference products dissolution in pH 5.5 medium are greater than 50, indicating the dissolution profiles are comparable.
- Test batch #H190066 shows higher variations (%RSD: (b) (4) %) at multiple time points than other two test batches (%RSD: (b) (4) % for batch #H190067 and (b) (4) % for batch #H190068) and RLD batches (%RSD: (b) (4) %). It should be noted that high values of %RSD for batch #H190066 were observed at only earlier time points (e.g., 5 -15 minutes).
- Raw data for test and reference batches as well as rejected runs were not submitted. The applicant will be asked to submit the missing information for further evaluation.
- Overall, the applicant's IVRT study is inadequate from BE perspective.

[32] https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm. Search 'Prednisolone Acetate'

4.6 Attachments

SAS Output

Study	SAS Data	SAS Code	SAS Output/Table
Particle Size Distribution	ANDA 216935.xlsx	PBE-PSD.SAS	CI_D10.doc CI_D50.doc CI_D90.doc CI_Span.doc

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 216935

APPLICANT: Lupin Limited

DRUG PRODUCT: Prednisolone Acetate Ophthalmic Suspension USP,1%

The Division of Bioequivalence III has completed its review and has identified the following deficiencies:

1. Please submit a method development and optimization report for your particle size distribution (PSD) testing to support all your selections of testing conditions/parameters and to justify the appropriateness of your method for PSD testing of Pred Forte® (prednisolone acetate) Ophthalmic Suspension, 1%.

2. In your in vitro drug release (IVRT) method development and optimization report (No. AMDR/PR47-DR-01/01), your reported f2 similarity values for batches PRS/2086/131B, PRS/2086/136, PRS/2086/137 and PRS/2086/138 were 44, 34, 40 and 37 (f2<50), respectively, demonstrating discriminatory ability; however f2 similarity values (f2>50) for process/formula variation batches PRS/2086/131A, PRS/2086/132, PRS/2086/133, PRS/2086/134 PRS/2086/135A and PRS/2086/135B were all above 50 (i.e., 60, 58, 59, 64, 51 and 70, respectively) and drug release for these batches was found to be comparable to your exhibit batch (H190068). Please explain and clarify discriminatory ability of the IVRT method based on your results.

3. In your IVRT study, you reported rejected sets. You stated: *"In two analytical runs of 12 units for each Test (Lot #H190068) and Reference (Lot #09634) were not in trend and variations were observed on % drug releases and these were investigated through the Analyst Check List for OOE i.e., DR/OOE/21/0005. The root cause is identified for low release and which was not in trend. And this happened due to improper precautions and wrong vial filled while analysis"*. However, you did not provide raw data for all analytical runs including the rejected runs. Please submit the missing information. In addition, please provide the investigation report if applicable on the rejected runs.

Sincerely yours,

April C. Braddy, Ph.D., RAC
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME

COMPLETED ASSIGNMENT FOR 216935 ID: 48756

Reviewer: Smith, Taylor **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Prednisolone Acetate Ophthalmic Suspension USP,1%

Items:

D	*Letter Date*	*Productivity Category*	*Sub Category*	*S re*	*Sub ta l*		
48756	4/11/2022	BIO	ANDA Original [1]	1	1	Edit	Delete
48756	4/11/2022	Parallel	In Vitro Studies (Other: IVIVC, GSD, QCRT) (Per study for all strengths) [1]	1	1	Edit	Delete
48756	4/11/2022	Parallel	Pre-Screening [0.25]	0.25	0.25	Edit	Delete
				Total	2.25		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216935

MICROBIOLOGY REVIEW(s)

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	
ANDA Number	216935
Assessment Cycle Number	1
Drug Product Name / Strength	Prednisolone Acetate Ophthalmic Suspension 1%
Route of Administration	Ophthalmic
Applicant Name	Lupin Pharmaceuticals
Manufacturing Site	Lupin Limited, Unit -2, Plot No. M-2 and M-2-1, Special Economic Zone, Phase – II Misc. Zone, Apparel Park, Dist. Dhar, Pithampur, Madhya Pradesh – 454775, India FEI Number: 3007549629
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

(b) (4)

(b) (4)

Document(s) Assessed	Date Received
0005	August 26, 2022
0002	April 11, 2022
0001	January 21, 2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The multidose ophthalmic drug product is a white to off-white milky fine suspension indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe. The product is (b) (4) (b) (4) filled into 10 mL and 15 mL sterile eye dropper bottles.

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

Supporting Documents:

- **A211806MR01.docx, dated 12/17/18 for review of gamma irradiation validation of container closures from STERIS (Report #: PQR/4/039-00)**

Select Number of Approved Comparability Protocols: 0
N/A

S DRUG SUBSTANCE

The drug substance Prednisolone Acetate is (b) (4) (b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

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

  The subject multidose ophthalmic drug product is a white to off-white milky fine suspension supplied in three configurations: 5 mL fill in 10 mL bottle, 10 mL fill in 15 mL bottle, and 15 mL fill in 15 mL bottle. (b) (4)
  (b) (4)

- **Drug product composition –**
  Section: 3.2.P.1 "Description and Composition of the Drug Product" p. 4 of 7 (Seq 0001)

Ingredient		Function
Prednisolone acetate*$ (b) (4) micronized)		
Benzalkonium Chloride (b) (4)	(b) (4)	
Edetate disodium (b) (4)		(b) (4)
Polysorbate 80		
Sodium Bisulfite		
Hypromellose (b) (4) (b) (4)		
Boric Acid		
Sodium Citrate (b) (4)		
Sodium Chloride		

Water for injection¥	(b) (4)

(b) (4)

(b) (4)

(b) (4)

32 Pages have been held in full as b4

(b) (4)

Executed Batch Records

Section: 3.2.R, Regional Information

Executed lot #(s): 5 mL fill in 10 mL bottle (H190063, H190064, H190065), 10 mL fill in 15 mL bottle (H190088), 15 mL fill in 15 mL bottle (H190069, H190070, H190071)

The batch records confirm that (b) (4)

(b) (4)

Assessment: ***Adequate***
The applicant has met the regulatory expectations regarding the executed batch records

(b) (4)

MICROBIOLOGY LIST OF DEFICIENCIES

Primary Microbiology Assessor Name and Date: Ryan Blower, Ph.D. 8/31/22
Secondary Assessor Name and Date: Bethanie Lee, Ph.D. 8/31/22

Ryan Blower

Digitally signed by Ryan Blower
Date: 9/01/2022 11:14:40AM
GUID: 6182a096000d5b27f286074cf2d986be

Bethanie Lee

Digitally signed by Bethanie Lee
Date: 9/01/2022 11:29:35AM
GUID: 5a9d84b3000e5ae45e6f6044896c5811

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 216935

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 216935

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior VP, Regulatory Affairs

Dear Kalpana Vanam:

This is in reference to your amendment received on May 10, 2024, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements.* The GDUFA goal date for review of this priority minor amendment is August 10, 2024.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Nimmy Mathews, Regulatory Project Manager, at (301) 796 - 9155.

Sincerely,

{See appended electronic signature page}

Nimmy Mathews
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

ANDA 216935

COMPLETE RESPONSE

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior VP, Regulatory Affairs

Dear Kalpana Vanam:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

We acknowledge receipt of the October 17, 2023 submission, which constituted a complete response to our December 7, 2022 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.

PHARMACEUTICAL QUALITY

Drug Substance

(b) (4)

Drug Product

(b) (4)

(b) (4)

Manufacturing

(b) (4)

a.

(b) (4)

b.

c.

d.

e. [redacted]

Biopharmaceutics

We noticed you proposed a new in vitro release (IVR) acceptance criteria [redacted] for IVR testing of Prednisolone Acetate Ophthalmic Suspension, USP, 1% using USP Apparatus 4 (flow through cell closed loop), at 8.0 mL/min in 150 mL phosphate buffer, pH 5.5 at 35 °C. However, the proposed acceptance criteria will [redacted]. If you agree to implement 'NLT [redacted]% in 10 minutes and NLT [redacted]% (Q) in 60 minutes' as the acceptance criteria for the product, [redacted]. Therefore, we request that you implement the recommended acceptance criteria 'NLT [redacted]% in 10 minutes and NLT [redacted]% (Q) in 60 minutes' for IVRT of Prednisolone Acetate Ophthalmic Suspension, USP, 1%.

Please update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

MICROBIOLOGY / BIOEQUIVALENCE / CLINICAL - COMPARATIVE ANALYSIS / 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.

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.

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 patents and 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
DRUG SUBSTANCE / DRUG PRODUCT / BIOPHARMACEUTICS / MANUFACTURING

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. Note that an amendment in response to a CRL classified by FDA as Minor that is submitted more than one year after the date FDA issued the CRL will be reclassified as a Major Amendment, except for ANDAs for products that are on the drug shortage list under section 506E of the FD&C Act (21 U.S.C. 356e), or are the subject of a response to a Public Health Emergency as declared by the Secretary of the U.S. Department of Health and Human Services under section 319 of the Public Health Service Act (PHS Act) (42 U.S.C. 247d), or are anticipated to be subject to the same criteria as apply to such a declaration, at the time of submission.

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. ANDAs that identify at least one facility that is referenced in an approved ANDA are subject to the self-identification requirement and to 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 (FDFs) or active pharmaceutical ingredients (APIs) 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.

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 provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to maximize the efficiency and utility of each assessment cycle, with the intent to reduce the number of assessment cycles for ANDAs and facilitate timely access to quality, affordable, safe, and effective generic medicines. 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.

As described in the *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions Draft Guidance for Industry*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon with the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, call Nimmy Mathews, Regulatory Project Manager, Division of Project Management, at (301) 796 - 9155.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
CAPT, United States Public Health Service
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).

ANDA 216935

INFORMATION REQUEST
QUALITY

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior VP, Regulatory Affairs

Dear Kalpana Vanam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

We also refer to your October 17, 2023 submission, containing your response to the December 7, 2022 Complete Response Letter.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

A. Biopharmaceutics

1. We noticed that you proposed a new in vitro release (IVR) acceptance criteria [redacted (b) (4)] for IVR testing of Prednisolone Acetate Ophthalmic Suspension, USP, 1% using *USP App 4 (flow through cell closed loop), at 8.0 mL/min in 150 mL phosphate buffer, pH 5.5 at 35°C*. However, the proposed acceptance criteria will [redacted (b) (4)] . If, however, you agree to implement *'NLT [redacted (b) (4)]% in 10 minutes and NLT [redacted (b) (4)]% (Q) in 60 minutes'* as the acceptance criteria for the product, [redacted (b) (4)] . Therefore, we request that you implement the

recommended acceptance criteria *'NLT (b)(4)% in 10 minutes and NLT (b)(4)% (Q) in 60 minutes'* for IVRT of Prednisolone Acetate Ophthalmic Suspension, USP, 1%.

Please update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a complete written response, no later than January 19, 2024 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. If you are responding to a late cycle information request[1], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. 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
MINOR

If you do not submit a complete written response by January 19, 2024, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Tristen Cook, Regulatory Business Process Manager, at tristen.cook@fda.hhs.gov or (240) 402 - 5934.

Sincerely,

{See appended electronic signature page}

Tristen Cook
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 216935

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior VP, Regulatory Affairs

Dear Kalpana Vanam:

This is in reference to your amendment received on October 17, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is April 17, 2024. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence was submitted and accepted, the GDUFA goal date for review of this priority major amendment is June 17, 2024. If FDA, upon assessment of a final bioequivalence study report submitted in the amendment, determines that an inspection of the relevant site or sites is necessary, the GDUFA goal date for review of this priority major amendment is August 17, 2024.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Nimmy Mathews, Regulatory Project Manager, at (301) 796 - 9155.

Sincerely,

{See appended electronic signature page}

Nimmy Mathews
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

ANDA 216935

COMPLETE RESPONSE

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior Vice President, Regulatory Affairs

Dear Kalpana Vanam:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

Reference is also made to any amendments submitted prior to the issuance of this letter.

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.

PHARMACEUTICAL QUALITY

Drug Substance

(b) (4)

Drug Product

(b) (4)

(b) (4)

1. (b) (4)
2.
3.
4.
5.
6.
7.

Manufacturing

The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon

receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility

1. (b) (4)

2.

Biopharmaceutics

We acknowledge the response to the IR comments dated July 28, 2022. We found your proposed in vitro release test (IVRT) method not acceptable for quality control of your proposed drug product, Prednisolone Acetate Ophthalmic Suspension USP, 1%. We recommend that the IVRT method [i.e., the method used to demonstrate in vitro bioequivalence (BE)] is adopted for Quality Control (QC) testing of your proposed drug product. Adopting a single method for BE demonstration and QC of the product enables the identification and rejection of variant batches of unacceptable quality (e.g., non-BE batches), based on the release profile comparison and appropriate establishment of the acceptance criterion.

Therefore, based on the totality of the submitted information, we recommend the following IVRT method and acceptance criteria for QC of the product:

IVRT method: 150 mL of pH 5.5 Phosphate Buffer @35 °C/USP IV (Flow through cell closed loop) at 8.0 mL/min.

Acceptance criteria: NMT (b) (4)% in 10 minutes and NLT (b) (4)% (Q) in 60 minutes.

Implement the recommended IVRT method and acceptance criteria and update the drug product release and stability specifications, and other parts of your ANDA submission, accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised release acceptance criteria in your stability program through your proposed expiry period. If drug release failures are observed on stability, they should be described. Discuss any corrective actions to avert such dissolution failures.

MICROBIOLOGY / BIOEQUIVALENCE / CLINICAL-COMPARATIVE ANALYSIS / 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.

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.

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 patents and exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. 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
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/MANUFACTURING/ BIOPHARMACEUTICS

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 (FDFs) or active pharmaceutical ingredients (APIs) 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 Nimmy Mathews, Regulatory Project Manager, Division of Project Management, at (301) 796 - 9155.

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).

ANDA 216935

DISCIPLINE REVIEW LETTER
QUALITY

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior Vice President, Regulatory Affairs

Dear Kalpana Vanam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Prednisolone Acetate Suspension USP, 1%.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance

1. (b) (4)
2.
3.

4. (b) (4)

B. Drug Product

1. (b) (4)

2.

2 Pages have been held in full as b4

12 (b) (4)

13

14

C. **Manufacturing**

a. Process

(b) (4)

3 Pages have been held in full as b4

D. Microbiology

1. No further comments at this time.

E. Biopharmaceutics

1. No further comments as this time.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than October 07, 2022. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
QUALITY

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Christina Pleas, Regulatory Business Process Manager, at Christina.Pleas@fda.hhs.gov or (240) 402 - 2873.

Sincerely,

{See appended electronic signature page}

Christina Pleas
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

ANDA 216935

DISCIPLINE REVIEW LETTER
LABELING

Lupin Limited
400 Campus Drive,
Somerset, New Jersey 08873
Attention: Ms. Kalpana Vanam
Senior Vice President, Regulatory Affairs

Dear Ms. Vanam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

Labeling deficiencies based on your submission received April 11, 2022:

1. CONTAINER LABEL
   a. Ensure that the cap color of your drug product is pink so that it follows the American Academy of Ophthalmology (AAO) packaging color-coding scheme. Refer to the American Academy of Ophthalmology (AAO) packaging color-coding.
   b. (b) (4)
   c. (b) (4)
   d. (b) (4)

2. CARTON LABELING
   (b) (4)

3. PRESCRIBING INFORMATION
   a. Reduce the title. to title case so that it reads as: "**Prednisolone Acetate Ophthalmic Suspension USP,1%**".
   b. (b) (4)

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

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

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

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

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

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than September 07, 2022. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

[1] GDUFAD Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Stacy Yoo, Labeling Project Manager, at Stacy.Yoo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Stacy Yoo, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 216935

DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior Vice President, Regulatory Affairs

Dear Kalpana Vanam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted pursuant to section 505(j) of the Federal Food,Drug, and Cosmetic Act (FD&C Act) for Prednisolone Acetate Ophthalmic Suspension USP,1%.

The following possible deficiencies have been identified by **BIOEQUIVALENCE**:

1. Please submit a method development and optimization report for your particle size distribution (PSD) testing to support all your selections of testing conditions/parameters and to justify the appropriateness of your method for PSD testing of Pred Forte® (prednisolone acetate) Ophthalmic Suspension, 1%.

2. In your in vitro drug release (IVRT) method development and optimization report (No. AMDR/PR47-DR-01/01), your reported f2 similarity values for batches PRS/2086/131B, PRS/2086/136, PRS/2086/137 and PRS/2086/138 were (b) (4) 7 (f2<50), respectively, demonstrating discriminatory ability; however f2 similarity values (f2>50) for process/formula variation batches PRS/2086/131A, PRS/2086/132, PRS/2086/133, PRS/2086/134 PRS/2086/135A and PRS/2086/135B were all (b) (4) 50 ((b) (4) respectively) and drug release for these batches was found to be comparable to your exhibit batch (H190068). Please explain and clarify discriminatory ability of the IVRT method based on your results.

3. In your IVRT study, you reported rejected sets. You stated: *"In two analytical runs of 12 units for each Test (Lot #H190068) and Reference (Lot #09634) were not in trend and variations were observed on % drug releases and these were investigated through the Analyst Check List for OOE i.e., DR/OOE/21/0005. The root cause is identified for* (b) (4) However, you did not provide raw data for all analytical runs including the rejected runs. Please submit the

missing information. In addition, please provide the investigation report if applicable on the rejected runs.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than **September 22, 2022**. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Chyong-Yi Wu, Bioequivalence Project Manager, at Chyong-Yi.Wu@fda.hhs.gov or (301) 796-4071.

Sincerely,

{See appended electronic signature page}

Chyong-Yi Wu, Ph.D.
OFFICE OF BIOEQUIVALENCE OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

INFROMATION REQUEST

ANDA 216935

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873

Attention: Kalpana Vanam
Senior Vice President, Regulatory Affairs

Dear Kalpana Vanam:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

Clinical:

Your submission remains under review, and we request additional information in order to complete our assessment.

In your Comparative Analyses report (Section 5.3.5.4) submitted April 11, 2022, you provided images and an annotated comparison of the labeling of the reference listed drug (RLD) compared to your proposed generic product. The labeling and images do not reflect the most recent revisions to the RLD product and labeling. Consistent with the American Academy of Ophthalmology's (AAO) recommendation for anti-inflammatory steroid drug products, the RLD has a pink cap. The most recent RLD labeling was approved on May 6, 2020.

We request that you submit:

1. High-resolution color photographs of your proposed generic drug product and the updated RLD product. Photos should include several angles of all aspects of the products and packaging, including photos of the dropper bottle and tip with and without cap removed.

2. A revised Comparative Analyses report comparing your product to the updated RLD product and labeling approved on May 6, 2020.

We request a complete written response no later than September 01, 2022 in order to continue our evaluation of your ANDA. 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

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

CLINICAL

If you do not submit a complete response by September 01, 2022, the review will be closed and the listed IRs may be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website.

If you have any questions, please contact the Clinical Project Manager, at Teena.Thomas@fda.hhs.gov

Please also confirm receipt of this letter.

Sincerely,

Teena Thomas, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Safety and Clinical Evaluation
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA 216935

INFORMATION REQUEST

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam
Senior Vice President, Regulatory Affairs

Dear Kalpana Vanam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 11, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Prednisolone Acetate Ophthalmic Suspension USP, 1%.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Microbiology

a. (b) (4)

1 Page has been held in full as b4

d. The gamma irradiation of primary container closures that is described in 3.2.P.3.5 is acknowledged. It is stated on page 23 of 268 of "Gamma Irradiation Sterilization – Report" that quarterly dose auditing and revalidation occurs. However, data from recent dose audits or a revalidation report was not provided. Please provide data from the most recent gamma irradiation dose verification audits of LDPE bottles/nozzles/caps used to package the commercial drug product.

e. The aseptic process simulation that is described in 3.2.P.3.5 is acknowledged. It is noted that validation was performed in 2018 and that no requalification is presented. Please provide media fill data from at least a single recent requalification run from the relevant line and container closure system. Data should include dates of performance, filling room/line used, volume of media fill, number of units filled, number of units incubated, number of units contaminated, duration of each fill, results of growth promotion studies, and filling speed.

We request a prompt written response, no later than August 26, 2022 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 Christina Pleas, Regulatory Business Process Manager, at Christina.Pleas@fda.hhs.gov or (240) 402 - 2873.

Sincerely,

{See appended electronic signature page}

Christina Pleas
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 216935

ACKNOWLEDGEMENT
ANDA RECEIPT

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited
400 Campus Drive
Somerset, NJ 08873
Attention: Kalpana Vanam

Dear Kalpana Vanam:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA or the Agency) has made a threshold determination that this ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Prednisolone Acetate Ophthalmic Suspension USP, 1%

DATE OF APPLICATION: April 11, 2022

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: April 11, 2022

This ANDA is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). Your request for a priority review of this submission meets the criteria listed in section 505(j)(11)(A) of the FD&C Act or the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements.* Also, your Pre-Submission Facility Correspondence was found eligible for further assessment and at the time of your ANDA submission the facility information was found complete and accurate. The GDUFA II goal date for review of this priority original ANDA is December 10, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to

date with the Agency's current thinking on topics through guidances for industry, including the Agency's recommendations reflected in relevant product specific guidances.

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

Prior to the action date of your ANDA or supplement to your application, we recommend you:

- Review the regulations that describe the requirements for National Drug Code(s) (NDC(s)) including the requirements for obtaining new NDC(s) and restrictions regarding the use of NDC(s) [see 21 CFR 207.33 and 21 CFR 207.35, respectively].
- Ensure that NDC(s) that appear on prescription drug labeling (e.g., Prescribing Information, outer packaging, carton labeling, container labeling) are assigned correctly per the above. CDER does not typically review the accuracy of NDC(s) on prescription drug labeling prior to approval.
- Optionally, reserve new NDC(s) by referring to the Drug Registration and Listing website or contacting eDRLS@fda.hhs.gov. Include the required additional data elements when converting the NDC reservation submission to a drug registration and listing submission when a drug is approved.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Nimmy Mathews, Regulatory Project Manager, at nimmy.mathews@fda.hhs.gov[1] or (301) 796 - 9155. We also recommend that you sign up for Generic Drug e-mail updates,[2] which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Bijal Patel, Pharm.D., BCPS
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

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[1] A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

[2] See FDA's Subscription Management Center at https://www.fda.gov/about-fda/contact-fda/get-email-updates