CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 208702

Name: Acyclovir Cream, 5%

Sponsor: Padagis Israel

Approval Date: February 04, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA028702Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

APPROVAL LETTER

ANDA 208702

ANDA APPROVAL

Paddock Laboratories, LLC
U.S. Agent for Perrigo UK FINCO Limited Partnership
3940 Quebec Avenue North
Minneapolis, MN 55427
Attention: Maureen Rath
Associate Director, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on January 7, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Acyclovir Cream, 5%.

Reference is also made to the complete response letter issued by this office on March 17, 2017, 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 is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Acyclovir Cream, 5%, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Zovirax Cream, 5%, of Valeant International Bermuda.

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

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

REPORTING REQUIREMENTS

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

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

All finished dosage forms (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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, Pharm.D.
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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

Sarah Kurtz

Digitally signed by Sarah Kurtz
Date: 2/04/2019 09:58:49AM
GUID: 54078879000a1b9e15dd31ed6f0343ca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

LABELING

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total length of tube
100 mm
unlaquered blank edge
1 mm
length available for printing plain surfaces
99 mm
overlap
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length available for printing texts (minus "text-free" edge for folding)
97 mm
text-free edge
2 mm
fold
(12-25 mm depending on the folding method)
0,5 mm overlap
2,5 mm text-free edge
41,5 mm circumference available for printing plain surfaces
37,5 mm circumference available for printing texts
2,5 mm text-free edge
Rx Only
NDC 45802-044-75
Acyclovir Cream, 5%
Each gram contains 50 mg acyclovir.
5g
USE ONLY FOR COLD SORES.
Perrigo®
Store at or below 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).
Usual Dosage: Apply 5 times per day for 4 days. See prescribing information for dosage information.
SEE CRIMP FOR LOT NO. AND EXPIRATION DATE.
FILLED BY WEIGHT, NOT BY VOLUME.
Made in Israel
Manufactured By Perrigo
Yeruham, Israel
Distributed By Perrigo
Allegan, MI 49010
Rev 03-16
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Store at or below 25°C (77°F); excursions permitted
to 15° to 30°C (59° to 86°F)
(see USP Controlled Room Temperature).
Usual Dosage: Apply 5 times per day for 4 days.
See prescribing information for dosage information.
Rx Only
NDC 45802-044-75
Acyclovir Cream, 5%
Each gram contains 50 mg acyclovir.
5 g
USE ONLY FOR COLD SORES.
Perrigo®
Acyclovir Cream, 5%
NDC 45802-044-75
5 g
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Made in Israel
Manufactured
By Perrigo
Yeruham, Israel
Distributed By
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www.perrigo.com
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Rx Only
NDC 45802-044-75
Acyclovir Cream, 5%
Each gram contains 50 mg acyclovir.
5 g
USE ONLY FOR COLD SORES.
Perrigo®
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACYCLOVIR CREAM safely and effectively. See full prescribing information for ACYCLOVIR CREAM.

ACYCLOVIR cream, for topical use

Initial U.S. Approval: 2002

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

Acyclovir Cream, 5% is a herpes simplex virus (HSV) nucleoside analogue DNA polymerase inhibitor indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------

- Apply five times a day for four days (2)
- Administer immediately following the onset of cold sore lesions (2)

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

- Topical cream containing 5% acyclovir (3)

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

- Acyclovir Cream is contraindicated in patients with known hypersensitivity to acyclovir, valacyclovir or any component of the formulation. (4)

----------WARNINGS AND PRECAUTIONS----------

- Only for topical use of recurrent HSV lesions on the external aspect of lips and the face. Acyclovir Cream should not be applied on mucous membranes including in the eye or inside the mouth or nose. (5)
- There is a potential for irritation and contact sensitization. (5)

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

- The most common adverse reactions reported were local skin reactions at the application site (6.1)
- Angioedema, anaphylaxis, contact dermatitis and eczema have been reported (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with Acyclovir Cream. Due to minimal systemic absorption of Acyclovir Cream, systemic drug interactions are unlikely. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 04/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Acyclovir Cream is a herpes simplex virus (HSV) nucleoside analogue DNA polymerase inhibitor indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

Acyclovir Cream should be applied five times per day for four days. Therapy should be initiated as early as possible following the onset of signs or symptoms of herpes labialis i.e., during the prodrome or when lesions appear.

For adolescents 12 years of age and older, the dosage is the same as in adults.

3 DOSAGE FORMS AND STRENGTHS

Each gram of Acyclovir Cream, 5% contains 50 mg of acyclovir.

4 CONTRAINDICATIONS

Acyclovir Cream is contraindicated in patients with known hypersensitivity to acyclovir, valacyclovir, or any component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 General

Acyclovir Cream should only be applied on the affected external aspects of the lips and face in patients with herpes labialis. Because no data are available, application to human mucous membranes is not recommended. Acyclovir Cream is intended for cutaneous use only and should not be used in the eye or inside the mouth or nose.

5.2 Contact Sensitization

Acyclovir Cream has a potential for irritation and contact sensitization [*see Adverse Reactions (6.1)*].

The effect of Acyclovir Cream has not been established in immunocompromised patients.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

In five double-blind, placebo-controlled trials, 1,124 patients were treated with acyclovir cream and 1,161 with placebo (vehicle) cream. Local application site reactions were reported by 5% of patients receiving acyclovir cream and 4% of patients receiving placebo. The most common adverse reactions at the site of topical application were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; each adverse reaction occurred in less than 1% of patients receiving acyclovir cream and placebo. Three patients on acyclovir cream and one patient on placebo discontinued treatment due to an adverse event.

An additional study, enrolling 22 healthy adults, was conducted to evaluate the dermal tolerance of acyclovir cream compared with vehicle using single occluded and semi-occluded patch testing methodology. Both acyclovir cream and placebo showed a high and cumulative irritation potential. Another study, enrolling 251 healthy adults, was conducted to evaluate the contact sensitization potential of acyclovir cream using repeat insult patch testing methodology. Of 202 evaluable subjects, possible cutaneous sensitization reactions were observed in the same 4 (2%) subjects with both acyclovir cream and placebo, and these reactions to both acyclovir cream and placebo were confirmed in 3 subjects upon rechallenge. The sensitizing ingredient(s) has not been identified.

The safety profile in patients 12 to 17 years of age was similar to that observed in adults.

6.2 Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of acyclovir cream. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to acyclovir cream.

General: Angioedema, anaphylaxis.

Skin: Contact dermatitis, eczema.

7 DRUG INTERACTIONS

Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with acyclovir cream. Due to minimal systemic absorption of acyclovir cream, systemic drug interactions are unlikely.

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CODE

PATIENT INFORMATION
Acyclovir (ay-SYE-kloe-vir) Cream, 5%

Important information: Acyclovir Cream is for use on cold sores on the lips and around the mouth only.
Acyclovir Cream should not be used in your eyes, mouth, nose, or on your genitals.

What is Acyclovir Cream?
- Acyclovir Cream is a prescription medicine used to treat cold sores (herpes labialis) that are recurring in adults and children 12 years of age and older, and who have normal immune systems.
- Acyclovir Cream is not a cure for cold sores.
- It is not known if Acyclovir Cream is safe and effective in children less than 12 years of age.

Who should not use Acyclovir Cream?
Do not use Acyclovir Cream if you are:
- allergic to Acyclovir Cream or any of the ingredients in Acyclovir Cream. See the end of this leaflet for a complete list of ingredients in Acyclovir Cream.

What should I tell my healthcare provider before using Acyclovir Cream?
Before using Acyclovir Cream, tell your healthcare provider about all of your medical conditions, including if you:
- become sick very easily (have a weak immune system)
- are pregnant or plan to become pregnant. It is not known if Acyclovir Cream will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Acyclovir Cream passes into your breast milk. You should not breastfeed if you have a cold sore near or on your breast.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use Acyclovir Cream?
- Use Acyclovir Cream exactly as your healthcare provider tells you to use it.
- Use Acyclovir Cream as soon as you have the first symptoms of a cold sore such as itching, redness, burning or tingling, or when the cold sore appears.
- Wash your hands with soap and water before and after applying Acyclovir Cream.
- The affected area should be clean and dry before applying Acyclovir Cream.
- Apply Acyclovir Cream to the affected area 5 times each day for 4 days, including the outer edge.
- You should not apply other skin products to the affected area during treatment with Acyclovir Cream.
- Do not rub the cold sore because this may cause the cold sore to spread to other areas around your mouth or make your cold sore worse.

What are the possible side effects of Acyclovir Cream?
The most common side effects of Acyclovir Cream are skin reactions at the treatment site and may include: dry or cracked lips, peeling, flaking or dryness of the skin, a burning or stinging feeling, and itching.
These are not all the possible side effects of Acyclovir Cream. Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088.

How should I store Acyclovir Cream?
- Store Acyclovir Cream at room temperature between 68°F to 77°F (20°C to 25°C).

Keep Acyclovir Cream and all medicines out of the reach of children.

General information about the safe and effective use of Acyclovir Cream
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Acyclovir Cream for a condition for which it was not prescribed.
Do not give Acyclovir Cream to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Acyclovir Cream that is written for health professionals.

What are the ingredients in Acyclovir Cream?
Active ingredient: acyclovir
Inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum

For more information, call Perrigo at 1-866-634-9120.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Made in Israel

Manufactured By Perrigo
Yeruham, Israel

Distributed By
Perrigo®
Allegan, MI 49010 • www.perrigo.com Rev 04-16 : 7G800 RC J1

(b) (4)

BACK

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled studies of acyclovir cream in pregnant women. Acyclovir cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Acyclovir was not teratogenic in the mouse, rabbit, or rat at exposures greatly in excess of human exposure.

8.3 Nursing Mothers

It is not known whether topically applied acyclovir is excreted in breast milk. Systemic exposure following topical administration is minimal.

However, after oral administration of acyclovir, acyclovir concentrations have been documented in breast milk in two women and ranged from 0.6 to 4.1 times the corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Nursing mothers who have active herpetic lesions near or on the breast should avoid nursing.

8.4 Pediatric Use

An open-label, uncontrolled trial with acyclovir cream, 5% was conducted in 113 patients aged 12 to 17 years with recurrent herpes labialis. In this trial, therapy was applied using the same dosing regimen as in adults and subjects were followed for adverse events. The safety profile was similar to that observed in adults. Safety and effectiveness in pediatric patients less than 12 years of age have not been established.

8.5 Geriatric Use

Clinical studies of acyclovir cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic absorption of acyclovir after topical administration is minimal [*see Clinical Pharmacology (12.3)*].

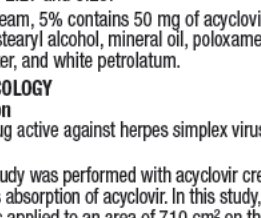
10 OVERDOSAGE

Overdosage by topical application of Acyclovir Cream is unlikely because of minimal systemic exposure [*see Clinical Pharmacology (12.3)*]. There is no information available for overdose.

11 DESCRIPTION

Acyclovir is a synthetic nucleoside analogue active against herpes viruses. Acyclovir Cream, 5% is a formulation for topical administration.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one; it has the following structural formula:



Acyclovir is a white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25.

Each gram of Acyclovir Cream, 5% contains 50 mg of acyclovir and the following inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Acyclovir is an antiviral drug active against herpes simplex virus [*see Microbiology (12.4)*].

12.3 Pharmacokinetics

A clinical pharmacology study was performed with acyclovir cream in adult volunteers to evaluate the percutaneous absorption of acyclovir. In this study, which included 6 male volunteers, the cream was applied to an area of 710 cm^2 on the backs of the volunteers 5 times daily at intervals of 2 hours for a total of 4 days. The weight of cream applied and urinary excretion of acyclovir were measured daily. Plasma concentration of acyclovir was assayed 1 hour after the final application. The average daily urinary excretion of acyclovir was approximately 0.04% of the daily applied dose. Plasma acyclovir concentrations were below the limit of detection (0.01 µM) in 5 subjects and barely detectable (0.014 µM) in 1 subject. Systemic absorption of acyclovir from acyclovir cream is minimal in adults.

The systemic absorption of acyclovir following topical application of cream has not been evaluated in patients <18 years of age.

12.4 Microbiology

Mechanism of Action: Acyclovir is a synthetic purine nucleoside analogue with cell culture and in vivo inhibitory activity against HSV types 1 (HSV-1) and 2 (HSV-2).

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In cell culture, acyclovir triphosphate stops replication of herpes viral DNA. This inhibition is accomplished in 3 ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase.

Antiviral Activity: The quantitative relationship between the cell culture susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (EC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the EC_{50} values against herpes simplex virus isolates range from 0.09 to 59.9 µM (0.02 to 13.5 µg/mL) for HSV-1 and from 0.04 to 44.0 µM (0.01 to 9.9 µg/mL) for HSV-2.

Drug Resistance: Resistance of HSV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Systemic exposure following topical administration of acyclovir is minimal. Dermal carcinogenicity studies were not conducted. Results from the studies of carcinogenesis, mutagenesis and fertility are not included in the full prescribing information for acyclovir cream due to the minimal exposures of acyclovir that result from dermal application. Information on these studies is available in the full prescribing information for acyclovir capsules, tablets, and suspension and acyclovir for injection.

14 CLINICAL STUDIES

14.1 Adult Subjects

Acyclovir cream was evaluated in two double-blind, randomized, placebo (vehicle)-controlled trials for the treatment of recurrent herpes labialis. The average patient had five episodes of herpes labialis in the previous 12 months. In the first trial, the median age of subjects was 37 years (range 18 to 81 years), 74% were female, and 94% were Caucasian. In the second trial, median age of subjects was 38 years (range 18 to 87 years), 73% were female, and 94% were Caucasian. Subjects were instructed to initiate treatment within one hour of noticing signs or symptoms and continue treatment for four days, with application of study medication five times per day. In both studies, the mean duration of the recurrent herpes labialis episode was approximately one-half day shorter in the subjects treated with acyclovir cream (n = 682) compared with subjects treated with placebo (n = 703) for approximately 4.5 days versus 5 days, respectively. No significant difference was observed between subjects receiving acyclovir cream or placebo in the prevention of progression of cold sore lesions.

14.2 Pediatric Subjects

An open-label, uncontrolled trial with acyclovir cream, 5% was conducted in 113 patients aged 12 to 17 years with recurrent herpes labialis. In this trial, therapy was applied using the same dosing regimen as in adults and subjects were followed for adverse events. The safety profile was similar to that observed in adults.

16 HOW SUPPLIED/STORAGE AND HANDLING

Acyclovir Cream is a white, odorless, smooth homogeneous cream. Each gram of Acyclovir Cream 5% contains 50 mg acyclovir in an aqueous cream base.
It is supplied as follows:

• 5 g tubes NDC 45802-044-75

Store at or below 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

General

Patients should be informed that Acyclovir Cream is a prescription topical cream for the treatment of cold sores (recurrent herpes labialis) that occur on the face and lips. Acyclovir Cream is not a cure for cold sores. Patients should be instructed that Acyclovir Cream is intended for cutaneous use only for herpes labialis of the lips and around the mouth. Patients should be advised that Acyclovir Cream should not be used in the eye, inside the mouth or nose, or on the genitals. Patients should be instructed to avoid applying other topical products to the affected area while using Acyclovir Cream.

Do not use if you are allergic to Acyclovir Cream or any of the ingredients in Acyclovir Cream. Before you use Acyclovir Cream, tell your doctor if you are pregnant, planning to become pregnant, or are breast-feeding.

Instructions for Use

Treatment should be initiated at the earliest sign or symptom of recurrence. Patients should be instructed to wash hands prior to application and ensure the face and/or lips are clean and dry. Patients should be advised to apply Acyclovir Cream topically five times per day for four days. Patients should be instructed to topically apply a quantity of Acyclovir Cream sufficient to cover the affected area, including the outer margin. Patients should be advised to avoid unnecessary rubbing of the affected area to avoid aggravating or transferring the infection. Patients should be instructed to wash their hands with soap and water after using Acyclovir Cream. Keep out of reach of children.

Possible Side Effects

Common skin-related side effects that occurred when acyclovir cream was applied include application site reactions. Acyclovir Cream has the potential for irritation and contact sensitization.

Made in Israel

Manufactured By Perrigo
Yeruham, Israel

Distributed By
Perrigo®
Allegan, MI 49010 • www.perrigo.com Rev 04-16 : 76800 RC J1

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

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	9/16/16
ANDA Number(s)	208702
Review Number	2
Applicant Name	Perrigo UK FINCO Limited Partnership
Established Name & Strength(s)	Acyclovir Cream, 5%
Proposed Proprietary Name	NA
Submission Received Date	4/5/16 (ECD response)
Labeling Reviewer	Esther Kim
Labeling Team Leader	Lisa Kwok

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

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

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

None

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated April 5, 2016.

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
None

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

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

LABELING HISTORY:

- **1/7/16:** Original ANDA 208702 received by FDA.
- **3/9/16:** Labeling Review #1 finalized with deficiencies for Container, Carton, Prescribing Information, and Patient Information.
- **3/28/16:** An ECD communication was sent to the applicant regarding deficiencies and recommendations.
- **4/5/16:** Resubmission in response to the ECD. This amendment is the subject of this review.

  From the 4/5/16 cover letter regarding labeling deficiencies and recommendations:

CONTAINER LABEL

FDA Comment 1:

Your proposed container labels lack adequate differentiation from your container labels under pending ANDA 205659. We recommend using colors that provide sufficient contrast for the strength statement and the "Rx Only" statement.

Perrigo Response 1:

Perrigo has changed the graphic colors of the container label and outer folding carton of ANDA #208702 Acyclovir Cream, 5% to colors that provide adequate differentiation from our container label and outer folding carton under pending ANDA 205659. Per FDA recommendation, the colors used provide sufficient contrast for the strength statement and the "Rx Only" statement.

CARTON LABELING

FDA Comment 2:

Refer to comment 1 above.

Perrigo Response 2:

See response to comment 1 above.

PRESCRIBING INFORMATION

FDA Comment 3:

a. HIGHLIGHTS OF PRESCRIBING INFORMATION

i. Limitation statement: Revise the presentation of the established name to appear in upper case letters as such: "These highlights do not include all the information needed to use ACYCLOVIR CREAM safely and effectively. See full prescribing information for ACYCLOVIR CREAM."

ii. Title: Please revise to read "ACYCLOVIR cream, for topical use". [Note the lower case "c" in "cream" and the removal of the strength following the established name.]

b. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED: Please add a description of the final product (i.e., white, odorless, smooth homogeneous cream) in this section.

Perrigo Response 3:

Perrigo's Prescribing Information labeling has been revised in accordance to the Agency's comments.

PATIENT INFORMATION

FDA Comment 4:

We recommend adding the phonetic spelling of the established name in the Title to be in accordance with the reference listed drug.

Perrigo Response 4:

Perrigo has added the phonetic spelling of the established name in the Title as per the Agency's comment.

Reviewer Comments:

The applicant has satisfactorily addressed the labeling deficiencies and recommendations for Container, Carton, Prescribing Information, and Patient Information.

We note the applicant has not submitted the SPL with this submission; however, their previous SPL submission (1/17/16) was found acceptable.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:

(b) (4)

[redacted]

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

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

Reviewer Comments:

None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 021478/S-007 **Supplement Approval Date:** 4/1/14 **Proprietary Name:** Zovirax **Established Name:** acyclovir cream **Description of Supplement:** This "Prior Approval" supplemental new drug application proposes the following: •Conversion of the labeling (package insert) per the final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," published January 24, 2006 (21 CFR parts 201.56, 201.57, and 201.80). •Update the Patient Information portion of labeling to be consistent with current Agency standards.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☒ **OTHER (Describe):** S-008 was approved 2/3/15 and provides for alternate drug substance and product manufacturers and an alternate testing facility.

Reviewer Assessment:

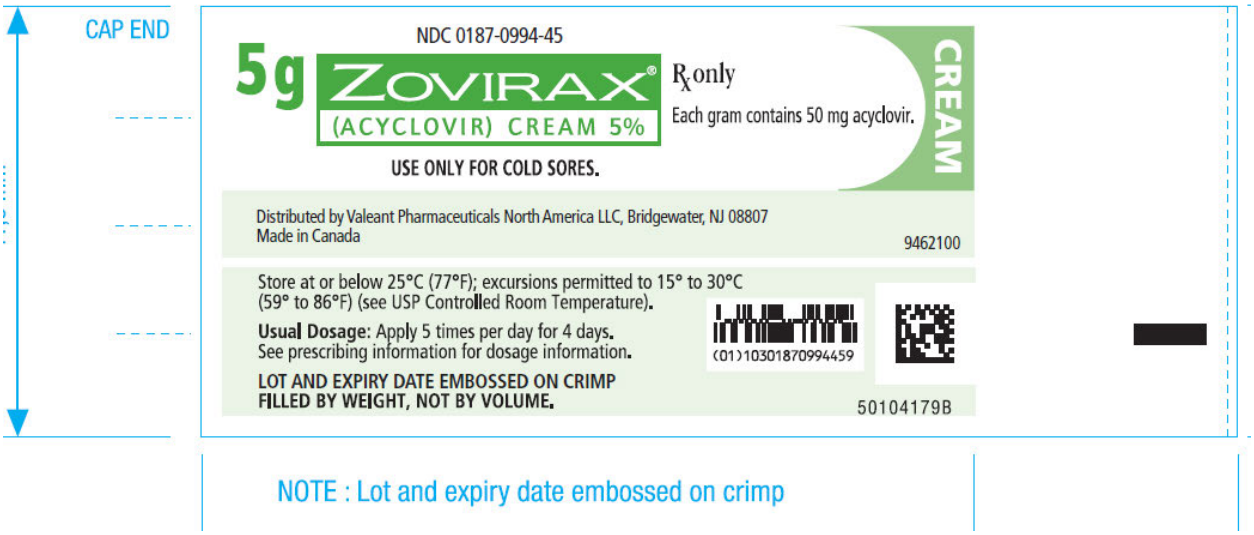
Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES** Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES** Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

None

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: Annual Report-13 DARRTS submission 2/26/16]



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

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

Table 2: USP and PF Search Results				
	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	9/16/2016	NO	NA	NA
PF	9/16/2016	NO	NA	NA

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/16/2016.

Table 3 provides Orange Book patents for the Model Labeling NDA 021478 and ANDA patent certifications.

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

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
NA						

Reviewer Assessment:

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

Reviewer Comments:

None

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

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

Reviewer Assessment:

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

Reviewer Comments:

None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each gram of Acyclovir Cream, 5% contains 50 mg of acyclovir and the following inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum.	**Each gram of Acyclovir Cream, 5% contains 50 mg of acyclovir and the following inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum.**	**No change**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each gram of Acyclovir Cream 5% contains 50 mg acyclovir in an aqueous cream base. Acyclovir Cream is supplied as follows: • 5 g tubes NDC 45802-044-75 Store at or below 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).	**Acyclovir Cream is a white, odorless, smooth homogeneous cream. Each gram of Acyclovir Cream 5% contains 50 mg acyclovir in an aqueous cream base. It is supplied as follows: • 5 g tubes NDC 45802-044-75 Store at or below 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).**	**The applicant added the description of the final product as requested in Labeling Review #1.**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Made in Israel Manufactured by Perrigo Yeruham 80500, Israel Distributed By Perrigo Allegan, MI 49010	**Made in Israel Manufactured by Perrigo Yeruham 80500, Israel Distributed By Perrigo® Allegan, MI 49010**	**The applicant revised the Distributed by statement to include the logo. This is acceptable.**

5. COMMENTS FOR CHEMISTRY REVIEWER

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

Reviewer Comments:
None

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:
None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	5 g tubes	4/5/16	Satisfactory
Blister	NA			
Carton	Final	1 x 5 g tube	4/5/16	Satisfactory
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	Revised: 04/ 2016	4/5/16	Satisfactory
Medication Guide	NA			
Patient Information	Final	Rev 04-16	4/5/16	Satisfactory
SPL Data Elements		Not submitted		

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 9/23/2016 11:24:42AM
GUID: 508da70800028c5cddf24c815a550d26

Esther Kim

Digitally signed by Esther Kim
Date: 9/16/2016 02:27:01PM
GUID: 5423006c00721ec9406da22c031498a2

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	3/9/16
ANDA Number(s)	208702
Review Number	1
Applicant Name	Perrigo UK FINCO Limited Partnership
Established Name & Strength(s)	Acyclovir Cream, 5%
Proposed Proprietary Name	NA
Submission Received Date	1/17/16 (original) 3/2/16 (amendment)
Labeling Reviewer	Esther Kim, Pharm.D.
Labeling Team Leader	Malik Imam

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

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

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

☐ On Policy Alert List

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on 3/9/16, based on your submission(s) dated 1/17/16 and 3/2/16:

1. CONTAINER LABEL
   Your proposed container labels lack adequate differentiation from your container labels under pending ANDA 205659. We recommend using colors that provide sufficient contrast for the strength statement and the "Rx Only" statement.

2. CARTON LABELING
   Refer to comment 1 above.

3. PRESCRIBING INFORMATION
   a. HIGHLIGHTS OF PRESCRIBING INFORMATION
      i. Limitation statement: Revise the presentation of the established name to appear in upper case letters as such: "**These highlights do not include all the information needed to use ACYCLOVIR CREAM safely and effectively. See full prescribing information for ACYCLOVIR CREAM**."
      ii. Title: Please revise to read "**ACYCLOVIR cream, for topical use**". [Note the lower case "c" in "cream" and the removal of the strength following the established name.]
   b. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED: Please add a description of the final product (i.e., white, odorless, smooth homogeneous cream) in this section.

4. PATIENT INFORMATION
   We recommend adding the phonetic spelling of the established name in the Title to be in accordance with the reference listed drug.

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

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

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

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

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

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

1.3 POST APPROVAL REVISIONS

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

None

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

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

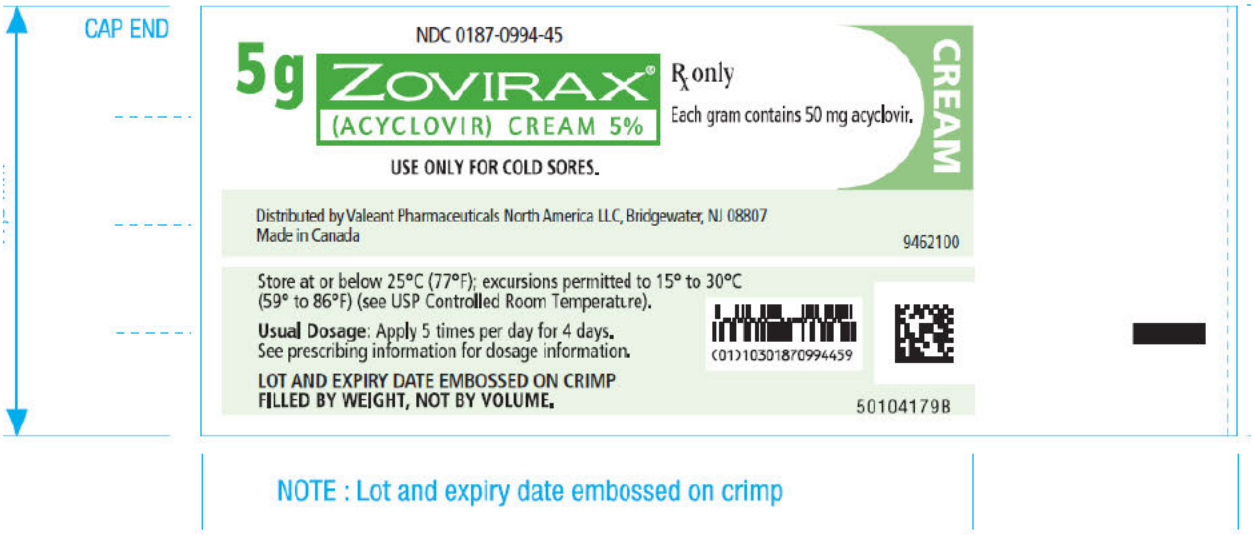
2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if original):** NDA 021478/S-007 **Supplement Approval Date:** 4/1/14 **Proprietary Name:** Zovirax Cream **Established Name:** acyclovir cream **Description of Supplement:** This "Prior Approval" supplemental new drug application proposes the following: •Conversion of the labeling (package insert) per the final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," published January 24, 2006 (21 CFR parts 201.56, 201.57, and 201.80). •Update the Patient Information portion of labeling to be consistent with current Agency standards.
☐ MOST RECENTLY APPROVED ANDA RLD LABELING **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out): Click here to enter text.
☒ OTHER (Describe): S-008 was approved 2/3/15 and provides for alternate drug substance and product manufacturers and an alternate testing facility. Labeling unaffected.

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: Annual Report-13 (2/26/16))



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

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

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	3/9/2016	NO	NA	NA
PF	3/9/2016	NO	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/9/2016.

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

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
NA						

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

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

2.5 MANUFACTURING FACILITY

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

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufactured (Cite Source)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
From 3.2.P.3 QOS: Perrigo Israel Pharmaceuticals Ltd. 1 Zvi Bornstein St. Industrial Zone Yeruham 8050315 Israel P.O. Box 306 Yeruham 8055201 Israel **FEI#**: 3001904238 **DUNS#**: 600093611	Container: Made in Israel Manufactured By Perrigo Yeruham 80500, Israel Distributed By Perrigo Allegan, MI 49010 Rev 11-15 Carton: Made in Israel Manufactured By Perrigo Yeruham 80500, Israel Distributed By Perrigo® Allegan, MI 49010 www.perrigo.com	Insert: Made in Israel Manufactured by Perrigo Yeruham 80500, Israel Distributed By Perrigo Allegan, MI 49010

3. ASSESSMENT OF ANDA LABELING AND LABELS

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

Is this product Rx or OTC? Please check one.

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

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

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

Reviewer Comments:
HIGHLIGHTS OF PRESCRIBING INFORMATION:
We will request the applicant revise the limitation statement and title.

3.1.1.1 RX: DESCRIPTION

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

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

<table>
<tr><th>Model Labeling Inactive Ingredients</th><th>ANDA Labeling Inactive Ingredients</th></tr>
<tr><td>Each gram of ZOVIRAX Cream, 5% contains 50 mg of acyclovir and the following inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum.</td><td>Each gram of Acyclovir Cream, 5% contains 50 mg of acyclovir and the following inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum.
From 3.2.P.1 QOS:
<table>
<tr><th rowspan="2">Ingredient</th><th rowspan="2">Function</th><th rowspan="2">Quality standard</th><th colspan="3">Quantity</th></tr>
<tr><th>g/5g tube</th><th>% (w/w)</th><th>ANDA and commercial batch (100 Kg) Kg</th></tr>
<tr><td colspan="6">ACTIVE:</td></tr>
<tr><td>Acyclovir</td><td>Active Ingredient</td><td>USP</td><td>0.25</td><td>5*</td><td>5*</td></tr>
<tr><td colspan="6">INACTIVE INGREDIENTS:</td></tr>
<tr><td>White Petrolatum, USP</td><td rowspan="8">(b) (4)</td><td>USP</td><td colspan="3" rowspan="8">(b) (4)</td></tr>
<tr><td>Cetostearyl Alcohol, NF</td><td>NF</td></tr>
<tr><td>Mineral Oil, USP</td><td>USP</td></tr>
<tr><td>Propylene Glycol, USP</td><td>USP</td></tr>
<tr><td>Sodium Lauryl Sulfate, NF</td><td>NF</td></tr>
<tr><td>Poloxamer 407, NF</td><td>NF</td></tr>
<tr><td>Purified Water (USP, EP)</td><td>USP</td></tr>
<tr><td colspan="3">TOTAL</td><td>5g</td><td>100%</td><td>100Kg</td></tr>
</table>
*Theoretical value. The actual amount is calculated according to the potency and the amount of water.</td></tr>
</table>

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling Memorandum of Understanding (MOU)?
YES, chemistry review pending

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

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

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

Reviewer Comments:
None

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

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

Table 7: Comparison of Model Labeling to ANDA Labeling

Model Labeling	Each gram of ZOVIRAX Cream 5% contains 50 mg acyclovir in an aqueous cream base. ZOVIRAX Cream is supplied as follows: • 5 g tubes NDC 0187-0994-45 Store at or below 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).
ANDA Labeling	Each gram of Acyclovir Cream 5% contains 50 mg acyclovir in an aqueous cream base. Acyclovir Cream is supplied as follows: • 5 g tubes NDC 45802-044-75 Store at or below 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

Reviewer Assessment:

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

Reviewer Comments:
We will recommend to the applicant to include a description of their drug product (i.e., white, odorless, smooth homogeneous cream).

3.1.2 RX: MEDICATION GUIDE

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

Reviewer Assessment:

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

Reviewer Comments:
None

3.1.3 RX: OTHER PATIENT LABELING

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

Reviewer Assessment:

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

Reviewer Comments:
We will request the applicant add the phonetic spelling of the established name to be in accordance with the RLD.

3.1.4 RX: CONTAINER LABEL

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

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

Reviewer Assessment:

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

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

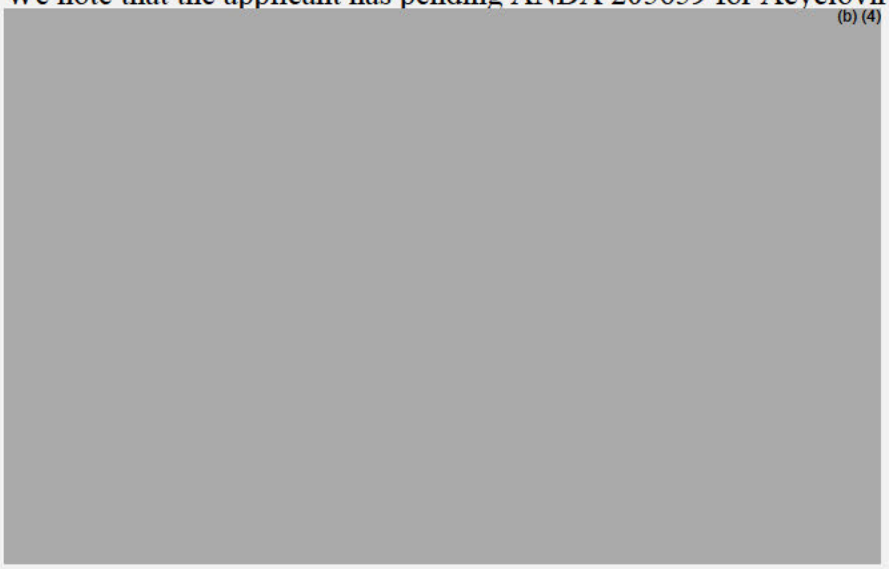
Is the following information properly displayed?

- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **YES**
- Warnings (if any) or cautionary statements (if any): **NA**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **NA**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **YES**
- Product strength equivalency statement: **NA**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**

For foreign manufacturers, does the labeling have the country of origin? **YES**
Are the required USP recommendations reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NO**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments:
We note that the applicant has pending ANDA 205659 for Acyclovir Ointment, 5%:



We will recommend the applicant revise the color scheme used to highlight the strength statement and "Rx Only" statement for subject ANDA as it is similar to the color scheme used for the ointment. We note that the RLD uses a green color scheme for the cream and a blue color scheme for the ointment.

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

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

Reviewer Assessment:

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

Reviewer Comments:
None

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

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

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**

Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
None

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

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

Reviewer Assessment:

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

Reviewer Comments:
None

3.1.5 RX: UNIT DOSE BLISTER LABEL

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

Reviewer Assessment:

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

Reviewer Comments:
None

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

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

Reviewer Assessment:

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

Reviewer Comments:
None

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**
Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **CLICK HERE**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **CLICK HERE**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **CLICK HERE**
Is the applicant's "exclusivity carve out" acceptable? **CLICK HERE**

Is the established name for this ANDA acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**

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

Is the following information properly displayed?

Pharmacological category: **CLICK HERE**
Net quantity statement: **CLICK HERE**
Route(s) of administration (other than oral): **CLICK HERE**
Warnings (if any) or cautionary statements (if any): **CLICK HERE**
NDC: **CLICK HERE**
Bar code per 21 CFR 201.25(c)(2): **CLICK HERE**

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

Reviewer Comments:
Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

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

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

Reviewer Assessment:

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

Reviewer Comments:
Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such

as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

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

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.2 OTC: OTHER PATIENT LABELING

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

Reviewer Assessment:

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

Reviewer Comments:
Click here to enter text.

3.3 CONTAINER/CLOSURE

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

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **NA**
Are the tamper evident requirements met for OTC and Controlled Substances? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **NA**

For ophthalmic products:

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

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**

If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**

What is the cap and ferrule color? **NA**

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

This topical product is not required to have a CRC.

From 3.2.P.7 QOS:

(b) (4)

[redacted]

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**

If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

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

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

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **CLICK HERE**

Are the stated contents in the table above acceptable? **CLICK HERE**

Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.

Did the chemistry reviewer verify the aluminum content? **CLICK HERE**

Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments:
None

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

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

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

Reviewer Assessment:

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

Reviewer Comments:
None

4. COMMENTS FOR CHEMISTRY REVIEWER

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

Reviewer Comments:
None

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:
None

6. SPECIAL CONSIDERATIONS

None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	5 g tubes	1/17/16	Revise
Blister	NA			
Carton	Draft	1 x 5 g tube	1/17/16	Revise
(Other – specify)	NA			
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	11/15	1/17/16	Revise

Medication Guide	NA			
Patient Information	Draft	11/15	1/17/16	Revise
SPL Data Elements		11/2015	1/17/16	Satisfactory

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

CHEMISTRY REVIEW(s)

Recommendation: Approval

ANDA 208702
Review #2

Drug Name/Dosage Form	ACYCLOVIR/OINTMENT
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	PERRIGO UK FINCO LTD PARTNERSHIP
US agent, if applicable	Dalit Fuchs, regulatoryaffairs.usa@perrigo.com

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original ANDA	*01/07/2016*	*All*
Quality-Response to IR	*03/02/2016*	*Drug Product/Process*
Response to ECD-Labeling	*04/05/2016*	*Labeling*
Quality-Quality Information/Bioequivalence	*06/01/2016*	*DBE*
Quality/Response to IR	*02/09/2017*	*Drug Product/Process*
Quality- CR Response	*8/24/2017*	*DBE/OPF*

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	N/A	N/A
Drug Product	Kumara Vadivel Subramanian	Richard Chang
Process	Youmin Wang	Maotang Zhou
Microbiology	N/A	N/A
Facility	Cassandra Abellard	Ying Zhang
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Jaimie Jones	
Application Technical Lead	Richard Chang	
Laboratory (OTR)	N/A	N/A

ORA Lead	N/A	N/A
Environmental	N/A	N/A

Quality Review Team

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	03/14/2018	Julia Pinto
	Type III *(if applicable)*					
	Type IV *(if applicable)*					
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS

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

Clinical	N/A			
Other	N/A			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is recommended for approval.

II. Summary of Quality Assessments

A. Product Overview

DMF (b) (4) for drug substance Acyclovir drug substance manufactured by (b) (4) is adequate (last reviewed by Julia Pinto on 03/14/2018). The drug substance is USP/EP compendial. Deficiencies identified in the previous review cycles have been adequately addressed. The drug product is a topical cream containing 5% w/w acyclovir, and (non)compendial. The applicant has provided information demonstrating Q3 attributes are equivalent to RLD as per product specific guidance on acyclovir cream. Deficiencies identified in the previous review cycles have been adequately addressed.

(b) (4)

A review of the application and inspectional documents of the facilities responsible for manufacturing Acyclovir 5% Cream per NDA 208702 has determined the facilities are acceptable at this time thus a recommendation of APPROVE is given for facilities.

Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee RC 01/30/2019	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee RC 01/30/2019	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee RC 01/30/2019	☐ Yes ☐ No *(see comments) ☒ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee RC 01/30/2019	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	Antiviral activity against herpesvirsuses
Duration of Treatment	4 days
Maximum Daily Dose	62.5 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Several high risk and medium risk items have been identified in the initial risk assessment (See attached).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

All high risk and medium risk items have been downgraded to low risk through specification control, clarification and process controls.

Risk Assessment- Acyclovir cream 5%.

PRODUCT PROPERTY/CQA	Initial RPN	Initial Comments	Risk Assessment after Review #1/IR#1	Justifications
Assay (Active)	18	Based on the initial risk algorithm		Stability data of API is well within the specification
Chemical Stability (All CQAs)	12	No apparent trending for their submitted stability data up to 18 months.		The CQA are well in in specification. No trends noted.
Bulk Content Uniformity	60			
Uniformity in Containers (includes USP <905> for single-dose)	45			
Microbial Limits	18			
Weight Loss	18			
pH	27			
Viscosity	48			
Physical Stability (API solid state in drug product)	60			
Physical Stability (Phase Separation/Sediment ation)	80			

(b) (4)

(b) (4)

PRODUCT PROPERTY/CQA	Initial RPN	Initial Comments	Risk Assessment after Review #1/IR#1	Justifications
				(b) (4)
Physical Stability (API Precipitation)	32			
API Particle Size (for suspensions)	48			
Particulate Size (for multi-phasic semi-solid products (e.g. emulsions, microspheres, liposomes, etc.))	64			
Water Activity	-			
Type of emulsion (e.g. o/w, w/o, w/o/w, o/w/o, o/w microemulsions, etc.)	64			
IVRT				

Richard Chang

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Date: 1/30/2019 05:13:45PM
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Recommendation: Approvable

A/NDA 208702
Review #1

Drug Name/Dosage Form	**ACYCLOVIR/OINTMENT**
Strength	**5%**
Route of Administration	**Topical**
Rx/OTC Dispensed	**Rx**
Applicant	**PERRIGO UK FINCO LTD PARTNERSHIP**
US agent, if applicable	**MAUREEN RATH**

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original ANDA	*01/07/2016*	*All*
Quality-Response to IR	*03/02/2016*	*Drug Product/Process*
Response to ECD-Labeling	*04/05/2016*	*Labeling*
Quality-Quality Information/Bioequivalence	*06/01/2016*	*DBE*
Quality/Response to IR	*02/09/2017*	*Drug Product/Process*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	**N/A**	**N/A**
Drug Product	**Kumara Vadivel Subramanian**	**Richard Chang**
Process	**Youmin Wang**	**Maotang Zhou**
Microbiology	**N/A**	**N/A**
Facility	**Cassandra Abellard**	**Derek Smith**
Biopharmaceutics	**N/A**	**N/A**
Regulatory Business Process Manager	**Filita Moore**	**N/A**
Application Technical Lead	**Richard Chang**	**N/A**
Laboratory (OTR)	**N/A**	**N/A**
ORA Lead	**N/A**	**N/A**

Environmental	N/A	N/A

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate with information request	03/02/2017	By M. Ethirajan
	Type III *(if applicable)*			Adequate information submitted with ANDA		
	Type IV *(if applicable)*					
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS: N/A

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

Clinical	N/A			
Other	N/A			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Based on Drug Product, Process and Facility Reviews, this ANDA is approvable.

II. Summary of Quality Assessments

A. Product Overview

Acyclovir is manufactured by [redacted] (b) (4) and the review of DMF is currently adequate. The drug substance, acyclovir has USP/EP monograph. The proposed DS specification is based on USP and DMF holder specification. The drug product, 5% w/w acyclovir dispersed into a cream base, is proposed for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older). Acyclovir Cream contains acyclovir plus excipients commonly used in topical preparation (e.g. propylene glycol, white petrolatum, cetostearyl alcohol, poloxamer 407, sodium lauryl sulfate, etc). Acyclovir Cream will be supplied in 5-gram collapsible aluminum tubes and closed with a polyethylene screw cap. Acyclovir cream 5% does not have USP monograph and the proposed DP release specification includes important critical drug product quality attributes such as appearance, identity, assay, impurities, pH, viscosity, uniformity of containers, microbial examination and residual solvents.

The test drug product of this ANDA meets the in vitro option requirements for Draft Guidance on Acyclovir Ointment (i.e. Q2/Q2 and required Q3 attributes, except that IVRT data submitted was reviewed by DBE and deemed inadequate (03/15/2017).

0	⇦ **Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	*For the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older)*
Duration of Treatment	*4 days*
Maximum Daily Dose	*62.5 mg*

Alternative Methods of Administration	*Not applicable*

B. Quality Assessment Overview

DMF (b) (4) was reviewed and deemed adequate with information request on 03/12/2017. The proposed DS specification is based on USP and DMF holder specification which includes all the critical quality attributes for drug substance. The drug product, Acyclovir cream 5% does not have USP monograph and the proposed DP release specification includes important critical drug product quality attributes. The risk for all test parameters was downgraded to low risk level. The test drug product of this ANDA meets the in vitro option requirements for Draft Guidance on Acyclovir Ointment (i.e. Q2/Q2 and required Q3 attributes).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

Risk of all the test parameters were downgraded to low risk level. Bulk uniformity issue was discussed in the process review and inclusion of such a test in the applicant's in-process specification with the limit of NMT (b) (4) RSD (b) (4) (b) (4)

Richard Chang

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Date: 3/15/2017 09:16:19AM
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Filita Moore

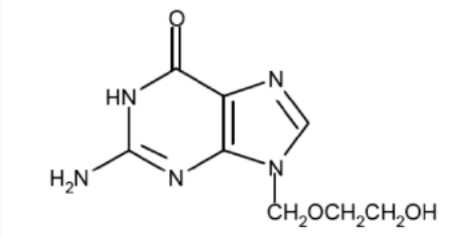
Digitally signed by Filita Moore
Date: 3/15/2017 04:16:51PM
GUID: 552ec52500a753138a90f7ba0d877e75

DRUG SUBSTANCE

Product Background: The active pharmaceutical ingredient (API), acyclovir, is a synthetic nucleoside analogue with antiviral activity against herpesviruses. Complete information on the synthesis and manufacturing controls for the drug substance is contained within the DMF (b) (4) Currently, DMF review is currently adequate with information request (Last review completed by M. Ethirajan dated 03/02/2017).

ANDA: 208702

Chemical Name and Structure:
6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- or
9-[(2-Hydroxyethoxy) methyl] guanine or



DMF # (if applicable): (b) (4)

Applicant Name/DMF Holder: (b) (4)

Review Summary:

Acyclovir is manufactured by (b) (4) and the review of DMF is currently adequate. The drug substance, acyclovir has USP/EP monograph. The proposed DS specification is based on USP and DMF holder specification which includes all the critical quality attributes for drug substance such as identification, assay, particle size and related substances. The ANDA applicant has provided drug substance information relevant to the drug product quality attributes. The proposed specifications for the Acyclovir are adequate to assure the identity, strength, purity and quality. Applicant has addressed minor deficiencies through IR#1 and no additional concerns noted. DMF (b) (4) was reviewed By Dr. M. Ethirajan and deemed adequate with information request on 03/12/2017.

List Submissions being reviewed (table):

New/ANDA (SD#1)-New ANDA- Expedited Review Request	1/7/2016
Quality – Response to IR	3/2/2016
Response to ECD- Labeling	4/5/2016
Quality-Quality Information / Bioequivalence	6/1/2016
Quality/Response to IR	2/9/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

Minor deficiencies in the drug substance release specification were identified and will be communicated to the applicant through IR letter. Applicant has responded to all the deficiencies and no additional issues noted.

S.1 General Information

Summary of the info provided. Information from Application

Physical description: White to off-white crystalline powder.

pKa: 9.35±0.20

Polymorphism:

According to a new article* there are six different crystal structures of Acyclovir.

(b) (4)

(b) (4)

(b) (4)

*Lutker KM, Quiñones R, Xu J, Ramamoorthy A, Matzger AJ. Polymorphs and Hydrates of Acyclovir. J Pharm Sci. 2011 March; 100(3): 949–963. [Pubmed: 21280051]
** *A. Dristl et al, Int J of Pharm., 139, 1996, 231-235*

Solubility: Soluble in diluted hydrochloric acid; slightly soluble in water; insoluble in alcohol.

Hygroscopicity: Acyclovir is nonhygroscopic.

Melting point: 256–257 ° C (J. Org. Chem. 1999, V. 64 (13), p. 4665 – 4668).

Chirality: The molecule does not have any stereogenic center.

Isomerism:

(b) (4)

Light Sensitivity: The product is not sensitive to sun light.

Partition Coefficient (n-octanol/water): -1.56 (according to USP MSDS)

Density: 1.77g/cm^3

Reviewer's Assessment: Satisfactory

Applicant provided all the relevant physiochemical properties of the drug substance. Based on the literature, it appears acyclovir has six polymorphs (b) (4) (b) (4) (b) (4) (b) (4)

(b) (4)

S.2 Manufacture

Commercial Synthetic Scheme and Process Flow Diagram

Reviewer's Assessment: Satisfactory

(b) (4)

Control of Materials

Reviewer's Assessment
Please refer DMF # (b) (4) for the relevant details.

Control of Critical Steps and Intermediates

Reviewer's Assessment:
Please refer DMF (b) (4) for the relevant details.

Summary of Process Validation Studies Conducted

Reviewer's Assessment:

Please refer DMF (b) (4) for the relevant details.

Summary of Manufacturing Process Development

Reviewer's Assessment:

Please refer DMF # (b) (4) for the relevant details.

S.3 Characterization

Summary of Elucidation of Structure Information

Reviewer's Assessment: Satisfactory

(b) (4)

Richard Chang

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Date: 3/12/2017 11:21:28AM
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Kumara Vadivel Subramanian

Digitally signed by Kumara Vadivel Subramanian
Date: 3/12/2017 09:47:20PM
GUID: 5407887b000a1c70265bc8c295333e76

PROCESS

Product Background:

ANDA: 208702

Drug Product Name / Strength: Acyclovir Cream USP, 5%

Route of Administration: Topical

Applicant Name: Perrigo Israel Pharmaceuticals Ltd

Review Summary:

(b) (4)

[redacted]

List Submissions being reviewed (table):

Document	Date
Original	01/07/2016
Quality/Response to Information Request	03/02/2016
Quality/Response to Information Request	02/09/2017

Highlight Key Outstanding Issues from Last Cycle: NA

Concise Description Outstanding Issues Remaining: The responses to the IR are acceptable. I am recommending approval from the process perspective.

P.3 Manufacture

Batch Formula

Quantitative Comparison between the Exhibit and Commercial Batch Formula

Ingredient	Function	Quality standard	Quantity		
			g/5g tube	% (w/w)	ANDA and commercial batch (100 Kg) Kg
ACTIVE:					
Acyclovir	Active Ingredient	USP	0.2500	5*	5*
INACTIVE INGREDIENTS:					
White Petrolatum, USP	(b) (4)	USP	(b) (4)		
Cetostearyl Alcohol, NF		NF			
Mineral Oil, USP		USP			
Propylene Glycol, USP		USP			
Sodium Lauryl Sulfate, NF		NF			
Poloxamer 407, NF		NF			
Purified Water (USP, EP)		USP			
TOTAL			**5g**	**100%**	**100Kg**

Reviewer's Assessment: Adequate

The commercial batch formula reflects the proposed composition and is consistent with the DP composition, MBR and executed BR. There is no overage.

Commercial Process Flow Diagram

A process flow diagram which illustrates the drug product manufacturing process unit operations is also provided below:

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(b) (4)

Summary of Process Validation Studies Conducted

Process validation will be conducted prior to marketing. Process validation information and data will be made available for the FDA inspection

Reviewer's Assessment: Adequate

No further comment is warranted.

Assessment of Microbiological Controls (as applicable)

Reviewer's Assessment: Not applicable

Comparability Protocols: None

Reviewer's Assessment: NA

Post-Approval Commitments

Reviewer's Assessment: NA

Lifecycle Management Considerations

NA

List of Deficiencies:

NA

Primary Process Reviewer Name and Date: Youmin Wang, 11/9/2016, 3/2/2017

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

Maotang Zhou

Youmin Wang

Digitally signed by Youmin Wang
Date: 3/03/2017 09:03:03AM
GUID: 508da704000288ee42ea39de4fcf7441

Maotang Zhou

Digitally signed by Maotang Zhou
Date: 3/03/2017 09:04:12AM
GUID: 508da72000029f940bf9150d4add500c

FACILITIES

Product Background: Treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.

NOTE: FIRST GENERIC

NDA 208702

Drug Product Name / Strength: Acyclovir Cream 5%

Route of Administration: Topical

Applicant Name: Perrigo UK Finco LTD Partnership

Review Summary: ADEQUATE – a review of the application and inspectional documents of the facilities responsible for manufacturing Acyclovir 5% Cream per NDA 208702 has determined that there are no significant outstanding issues with the firms involved in the manufacturing of the product. No pre-approval inspections were conducted.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
eCTD 0003	06/01/2016	Quality/ Quality Information
eCTD 0001	03/02/2016	Quality/ Response to IR
eCTD 0000	01/07/2016	New/NDA

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

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QUALITY ASSESSMENT

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Reviewer's Assessment: N/A

List of Deficiencies:

Reviewer's Assessment: N/A

Primary Facilities Reviewer Name and Date:

C. Abellard 12/01/2016

Consumer Safety Officer, OPF/DIA- BII

Secondary Reviewer Name and Date:

Derek S. Smith, Ph.D. 02/03/2017

Derek Smith

Digitally signed by Derek Smith
Date: 2/03/2017 12:23:47PM
GUID: 508da7480002bfe5d5fe14a12da3599d

Cassandra Abellard

Digitally signed by Cassandra Abellard
Date: 1/13/2017 09:11:36AM
GUID: 564f42da0022c9f20052124ea8956e48

Richard Chang

Digitally signed by Richard Chang
Date: 3/16/2017 08:59:11AM
GUID: 508da701000286e9caa589ba477de0b4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

BIOEQUIVALENCE REVIEW(s)

Recommendation: Approval

ANDA 208702
Review #2

Drug Name/Dosage Form	ACYCLOVIR/OINTMENT
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	PERRIGO UK FINCO LTD PARTNERSHIP
US agent, if applicable	Dalit Fuchs, regulatoryaffairs.usa@perrigo.com

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original ANDA	*01/07/2016*	*All*
Quality-Response to IR	*03/02/2016*	*Drug Product/Process*
Response to ECD-Labeling	*04/05/2016*	*Labeling*
Quality-Quality Information/Bioequivalence	*06/01/2016*	*DBE*
Quality/Response to IR	*02/09/2017*	*Drug Product/Process*
Quality- CR Response	*8/24/2017*	*DBE/OPF*

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	N/A	N/A
Drug Product	Kumara Vadivel Subramanian	Richard Chang
Process	Youmin Wang	Maotang Zhou
Microbiology	N/A	N/A
Facility	Cassandra Abellard	Ying Zhang
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Jaimie Jones	
Application Technical Lead	Richard Chang	
Laboratory (OTR)	N/A	N/A

ORA Lead	N/A	N/A
Environmental	N/A	N/A

Quality Review Team

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	03/14/2018	Julia Pinto
	Type III *(if applicable)*					
	Type IV *(if applicable)*					
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS

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

Clinical	N/A			
Other	N/A			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is recommended for approval.

II. Summary of Quality Assessments

A. Product Overview

DMF (b) (4) for drug substance Acyclovir drug substance manufactured by (b) (4) is adequate (last reviewed by Julia Pinto on 03/14/2018). The drug substance is USP/EP compendial. Deficiencies identified in the previous review cycles have been adequately addressed. The drug product is a topical cream containing 5% w/w acyclovir, and (non)compendial. The applicant has provided information demonstrating Q3 attributes are equivalent to RLD as per product specific guidance on acyclovir cream. Deficiencies identified in the previous review cycles have been adequately addressed.

(b) (4)

A review of the application and inspectional documents of the facilities responsible for manufacturing Acyclovir 5% Cream per NDA 208702 has determined the facilities are acceptable at this time thus a recommendation of APPROVE is given for facilities.

Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee RC 01/30/2019	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee RC 01/30/2019	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee RC 01/30/2019	☐ Yes ☐ No *(see comments) ☒ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee RC 01/30/2019	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	Antiviral activity against herpesvirsuses
Duration of Treatment	4 days
Maximum Daily Dose	62.5 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Several high risk and medium risk items have been identified in the initial risk assessment (See attached).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

All high risk and medium risk items have been downgraded to low risk through specification control, clarification and process controls.

Risk Assessment- Acyclovir cream 5%.

PRODUCT PROPERTY/CQA	Initial RPN	Initial Comments	Risk Assessment after Review #1/IR#1	Justifications
Assay (Active)	18	Based on the initial risk algorithm		Stability data of API is well within the specification
Chemical Stability (All CQAs)	12	No apparent trending for their submitted stability data up to 18 months.		The CQA are well in in specification. No trends noted.
Bulk Content Uniformity	60			
Uniformity in Containers (includes USP <905> for single-dose)	45			
Microbial Limits	18			
Weight Loss	18			
pH	27			
Viscosity	48			
Physical Stability (API solid state in drug product)	60			
Physical Stability (Phase Separation/Sediment ation)	80			

(b) (4)

(b) (4)

PRODUCT PROPERTY/CQA	Initial RPN	Initial Comments	Risk Assessment after Review #1/IR#1	Justifications
				(b) (4)
Physical Stability (API Precipitation)	32			
API Particle Size (for suspensions)	48			
Particulate Size (for multi-phasic semi-solid products (e.g. emulsions, microspheres, liposomes, etc.))	64			
Water Activity	-			
Type of emulsion (e.g. o/w, w/o, w/o/w, o/w/o, o/w microemulsions, etc.)	64			
IVRT				

Richard Chang

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Recommendation: Approvable

A/NDA 208702
Review #1

Drug Name/Dosage Form	**ACYCLOVIR/OINTMENT**
Strength	**5%**
Route of Administration	**Topical**
Rx/OTC Dispensed	**Rx**
Applicant	**PERRIGO UK FINCO LTD PARTNERSHIP**
US agent, if applicable	**MAUREEN RATH**

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original ANDA	*01/07/2016*	*All*
Quality-Response to IR	*03/02/2016*	*Drug Product/Process*
Response to ECD-Labeling	*04/05/2016*	*Labeling*
Quality-Quality Information/Bioequivalence	*06/01/2016*	*DBE*
Quality/Response to IR	*02/09/2017*	*Drug Product/Process*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	**N/A**	**N/A**
Drug Product	**Kumara Vadivel Subramanian**	**Richard Chang**
Process	**Youmin Wang**	**Maotang Zhou**
Microbiology	**N/A**	**N/A**
Facility	**Cassandra Abellard**	**Derek Smith**
Biopharmaceutics	**N/A**	**N/A**
Regulatory Business Process Manager	**Filita Moore**	**N/A**
Application Technical Lead	**Richard Chang**	**N/A**
Laboratory (OTR)	**N/A**	**N/A**
ORA Lead	**N/A**	**N/A**

Environmental	N/A	N/A

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate with information request	03/02/2017	By M. Ethirajan
	Type III *(if applicable)*			Adequate information submitted with ANDA		
	Type IV *(if applicable)*					
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS: N/A

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

Clinical	N/A			
Other	N/A			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Based on Drug Product, Process and Facility Reviews, this ANDA is approvable.

II. Summary of Quality Assessments

A. Product Overview

Acyclovir is manufactured by [redacted] (b) (4) and the review of DMF is currently adequate. The drug substance, acyclovir has USP/EP monograph. The proposed DS specification is based on USP and DMF holder specification. The drug product, 5% w/w acyclovir dispersed into a cream base, is proposed for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older). Acyclovir Cream contains acyclovir plus excipients commonly used in topical preparation (e.g. propylene glycol, white petrolatum, cetostearyl alcohol, poloxamer 407, sodium lauryl sulfate, etc). Acyclovir Cream will be supplied in 5-gram collapsible aluminum tubes and closed with a polyethylene screw cap. Acyclovir cream 5% does not have USP monograph and the proposed DP release specification includes important critical drug product quality attributes such as appearance, identity, assay, impurities, pH, viscosity, uniformity of containers, microbial examination and residual solvents.

The test drug product of this ANDA meets the in vitro option requirements for Draft Guidance on Acyclovir Ointment (i.e. Q2/Q2 and required Q3 attributes, except that IVRT data submitted was reviewed by DBE and deemed inadequate (03/15/2017).

0	⇦ **Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	*For the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older)*
Duration of Treatment	*4 days*
Maximum Daily Dose	*62.5 mg*

Alternative Methods of Administration	*Not applicable*

B. Quality Assessment Overview

DMF (b) (4) was reviewed and deemed adequate with information request on 03/12/2017. The proposed DS specification is based on USP and DMF holder specification which includes all the critical quality attributes for drug substance. The drug product, Acyclovir cream 5% does not have USP monograph and the proposed DP release specification includes important critical drug product quality attributes. The risk for all test parameters was downgraded to low risk level. The test drug product of this ANDA meets the in vitro option requirements for Draft Guidance on Acyclovir Ointment (i.e. Q2/Q2 and required Q3 attributes).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

Risk of all the test parameters were downgraded to low risk level. Bulk uniformity issue was discussed in the process review and inclusion of such a test in the applicant's in-process specification with the limit of NMT (b) (4) RSD (b) (4) (b) (4)

Richard Chang

Digitally signed by Richard Chang
Date: 3/15/2017 09:16:19AM
GUID: 508da701000286e9caa589ba477de0b4

Filita Moore

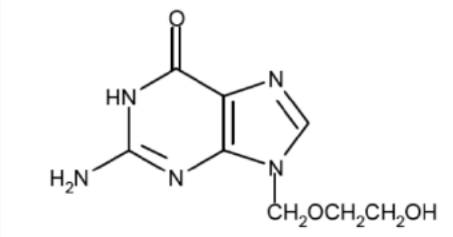
Digitally signed by Filita Moore
Date: 3/15/2017 04:16:51PM
GUID: 552ec52500a753138a90f7ba0d877e75

DRUG SUBSTANCE

Product Background: The active pharmaceutical ingredient (API), acyclovir, is a synthetic nucleoside analogue with antiviral activity against herpesviruses. Complete information on the synthesis and manufacturing controls for the drug substance is contained within the DMF (b) (4) Currently, DMF review is currently adequate with information request (Last review completed by M. Ethirajan dated 03/02/2017).

ANDA: 208702

Chemical Name and Structure:
6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]- or
9-[(2-Hydroxyethoxy) methyl] guanine or



DMF # (if applicable): (b) (4)

Applicant Name/DMF Holder: (b) (4)

Review Summary:

Acyclovir is manufactured by (b) (4) and the review of DMF is currently adequate. The drug substance, acyclovir has USP/EP monograph. The proposed DS specification is based on USP and DMF holder specification which includes all the critical quality attributes for drug substance such as identification, assay, particle size and related substances. The ANDA applicant has provided drug substance information relevant to the drug product quality attributes. The proposed specifications for the Acyclovir are adequate to assure the identity, strength, purity and quality. Applicant has addressed minor deficiencies through IR#1 and no additional concerns noted. DMF (b) (4) was reviewed By Dr. M. Ethirajan and deemed adequate with information request on 03/12/2017.

List Submissions being reviewed (table):

New/ANDA (SD#1)-New ANDA- Expedited Review Request	1/7/2016
Quality – Response to IR	3/2/2016
Response to ECD- Labeling	4/5/2016
Quality-Quality Information / Bioequivalence	6/1/2016
Quality/Response to IR	2/9/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

Minor deficiencies in the drug substance release specification were identified and will be communicated to the applicant through IR letter. Applicant has responded to all the deficiencies and no additional issues noted.

S.1 General Information

Summary of the info provided. Information from Application

Physical description: White to off-white crystalline powder.

pKa: 9.35±0.20

Polymorphism:

According to a new article* there are six different crystal structures of Acyclovir.

(b) (4)

(b) (4)

(b) (4)

*Lutker KM, Quiñones R, Xu J, Ramamoorthy A, Matzger AJ. Polymorphs and Hydrates of Acyclovir. J Pharm Sci. 2011 March; 100(3): 949–963. [Pubmed: 21280051]
** *A. Dristl et al, Int J of Pharm., 139, 1996, 231-235*

Solubility: Soluble in diluted hydrochloric acid; slightly soluble in water; insoluble in alcohol.

Hygroscopicity: Acyclovir is nonhygroscopic.

Melting point: 256–257 ° C (J. Org. Chem. 1999, V. 64 (13), p. 4665 – 4668).

Chirality: The molecule does not have any stereogenic center.

Isomerism:

(b) (4)

Light Sensitivity: The product is not sensitive to sun light.

Partition Coefficient (n-octanol/water): -1.56 (according to USP MSDS)

Density: 1.77g/cm^3

Reviewer's Assessment: Satisfactory

Applicant provided all the relevant physiochemical properties of the drug substance. Based on the literature, it appears acyclovir has six polymorphs (b) (4) (b) (4) (b) (4) (b) (4)

(b) (4)

S.2 Manufacture

Commercial Synthetic Scheme and Process Flow Diagram

Reviewer's Assessment: Satisfactory

(b) (4)

Control of Materials

Reviewer's Assessment
Please refer DMF # (b) (4) for the relevant details.

Control of Critical Steps and Intermediates

Reviewer's Assessment:
Please refer DMF (b) (4) for the relevant details.

Summary of Process Validation Studies Conducted

Reviewer's Assessment:

Please refer DMF (b) (4) for the relevant details.

Summary of Manufacturing Process Development

Reviewer's Assessment:

Please refer DMF # (b) (4) for the relevant details.

S.3 Characterization

Summary of Elucidation of Structure Information

Reviewer's Assessment: Satisfactory

(b) (4)

Richard Chang

Digitally signed by Richard Chang
Date: 3/12/2017 11:21:28AM
GUID: 508da701000286e9caa589ba477de0b4

Kumara Vadivel Subramanian

Digitally signed by Kumara Vadivel Subramanian
Date: 3/12/2017 09:47:20PM
GUID: 5407887b000a1c70265bc8c295333e76

PROCESS

Product Background:

ANDA: 208702

Drug Product Name / Strength: Acyclovir Cream USP, 5%

Route of Administration: Topical

Applicant Name: Perrigo Israel Pharmaceuticals Ltd

Review Summary:

(b) (4)

[redacted]

List Submissions being reviewed (table):

Document	Date
Original	01/07/2016
Quality/Response to Information Request	03/02/2016
Quality/Response to Information Request	02/09/2017

Highlight Key Outstanding Issues from Last Cycle: NA

Concise Description Outstanding Issues Remaining: The responses to the IR are acceptable. I am recommending approval from the process perspective.

P.3 Manufacture

Batch Formula

Quantitative Comparison between the Exhibit and Commercial Batch Formula

Ingredient	Function	Quality standard	Quantity		
			g/5g tube	% (w/w)	ANDA and commercial batch (100 Kg) Kg
ACTIVE:					
Acyclovir	Active Ingredient	USP	0.2500	5*	5*
INACTIVE INGREDIENTS:					
White Petrolatum, USP	(b) (4)	USP	(b) (4)		
Cetostearyl Alcohol, NF		NF			
Mineral Oil, USP		USP			
Propylene Glycol, USP		USP			
Sodium Lauryl Sulfate, NF		NF			
Poloxamer 407, NF		NF			
Purified Water (USP, EP)		USP			
TOTAL			**5g**	**100%**	**100Kg**

Reviewer's Assessment: Adequate

The commercial batch formula reflects the proposed composition and is consistent with the DP composition, MBR and executed BR. There is no overage.

Commercial Process Flow Diagram

A process flow diagram which illustrates the drug product manufacturing process unit operations is also provided below:

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

(b) (4)

Summary of Process Validation Studies Conducted

Process validation will be conducted prior to marketing. Process validation information and data will be made available for the FDA inspection

Reviewer's Assessment: Adequate

No further comment is warranted.

Assessment of Microbiological Controls (as applicable)

Reviewer's Assessment: Not applicable

Comparability Protocols: None

Reviewer's Assessment: NA

Post-Approval Commitments

Reviewer's Assessment: NA

Lifecycle Management Considerations

NA

List of Deficiencies:

NA

Primary Process Reviewer Name and Date: Youmin Wang, 11/9/2016, 3/2/2017

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

Maotang Zhou

Youmin Wang

Digitally signed by Youmin Wang
Date: 3/03/2017 09:03:03AM
GUID: 508da704000288ee42ea39de4fcf7441

Maotang Zhou

Digitally signed by Maotang Zhou
Date: 3/03/2017 09:04:12AM
GUID: 508da72000029f940bf9150d4add500c

FACILITIES

Product Background: Treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.

NOTE: FIRST GENERIC

NDA 208702

Drug Product Name / Strength: Acyclovir Cream 5%

Route of Administration: Topical

Applicant Name: Perrigo UK Finco LTD Partnership

Review Summary: ADEQUATE – a review of the application and inspectional documents of the facilities responsible for manufacturing Acyclovir 5% Cream per NDA 208702 has determined that there are no significant outstanding issues with the firms involved in the manufacturing of the product. No pre-approval inspections were conducted.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
eCTD 0003	06/01/2016	Quality/ Quality Information
eCTD 0001	03/02/2016	Quality/ Response to IR
eCTD 0000	01/07/2016	New/NDA

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

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

QUALITY ASSESSMENT

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Reviewer's Assessment: N/A

List of Deficiencies:

Reviewer's Assessment: N/A

Primary Facilities Reviewer Name and Date:

C. Abellard 12/01/2016

Consumer Safety Officer, OPF/DIA- BII

Secondary Reviewer Name and Date:

Derek S. Smith, Ph.D. 02/03/2017

Derek Smith

Digitally signed by Derek Smith
Date: 2/03/2017 12:23:47PM
GUID: 508da7480002bfe5d5fe14a12da3599d

Cassandra Abellard

Digitally signed by Cassandra Abellard
Date: 1/13/2017 09:11:36AM
GUID: 564f42da0022c9f20052124ea8956e48

Richard Chang

Digitally signed by Richard Chang
Date: 3/16/2017 08:59:11AM
GUID: 508da701000286e9caa589ba477de0b4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ADDENDUM

ANDA No.	208702	
Drug Product Name	Acyclovir Cream	
Strength(s)	5%	
Applicant Name	Perrigo UK Finco Ltd Partnership	
Applicant Address	Wrafton, Braunton Devon, EX33 2DL UK	
US Contact Name and US Mailing Address	Maureen Rath, Associate Director, Regulatory Affairs Paddock Laboratories, LLC, a Perrigo Company 3940 Quebec Avenue North Minneapolis, MN 55427 regulatoryaffairs.usa@perrigo.com	
US Contact Telephone Number	(763) 732-0235	
US Contact Fax Number	(763) 732-0509	
Original Submission Date(s)	1/7/2016	
Submission Date(s) of Amendment(s) Under Review	08/24/2017	
Primary Reviewer	Li Li, Ph.D.	
Secondary Reviewer	Anil K. Nair, Ph.D.	
Tertiary Reviewer	N/A	
Study Number(s)	R&D Document :#68024	PER-AR-005-15-R00
Study Type(s)	In Vitro Drug Release Test	In Vitro Skin Permeation Test
Strength(s)	5%	5%
Analytical Site	Perrigo Israel Pharmaceuticals Ltd.	(b) (4)
Analytical Site Address	1 Zvi Bornstein St., Industrial Zone, Yeruham 8050315, Israel	
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☒ **Complete**
Formulation	☒ **Adequate** ☐ **Inadequate**	
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**	
Deficiency Classification	☐ **Major** ☐ **Minor/IR**	

	☒ **N/A (Review is Adequate)**		
Major Deficiency Theme	**N/A**		
Justification for Major Designation	**N/A**		
Overall Review Result	☒ **Adequate as per the DCR's decision based on the totality of information in the application** ☐ **Inadequate**		
Product Specific Guidance (PSG) Referenced in Review	☒ **Recommended/Latest Revision Date: December 2016** **RLD Number: NDA 021478** ☐ **N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO** **This review follows the revised/new guidance (December 2016)**		
Communication	☐ **ECD** ☐ **IR** ☒ **Not Applicable**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	Formulation (Q1/Q2)	5%	☒ **Adequate** ☐ **Inadequate**
1, 4	In Vitro Drug Release Test	5%	☒ **Adequate** ☐ **Inadequate**
1	In Vitro Skin Permeation Test	5%	☐ **Adequate** ☒ **Inadequate**
1	Physicochemical Characterization (Q3)	5%	☒ **Adequate** ☐ **Inadequate** (based on drug quality review[3])

1 EXECUTIVE SUMMARY

This is an addendum to the previous BE review[1].

The current product-specific Draft Guidance (PSG, revised Dec 2016) for Acyclovir Cream, 5%, recommends an in vitro or in vivo option to determine bioequivalence (BE) between test and RLD product.

In the original submission in January 2016, Perrigo took the in vitro approach and requested a waiver of *in vivo* BE study for Acyclovir Cream, 5%. To support its request, the applicant submitted the following information: 1) test product formulation; 2) comparative physicochemical characterization of the test and RLD formulations; 3) comparative *in vitro* drug release test (IVRT) of acyclovir from the test and RLD formulations and 4) comparative *in vitro* skin permeation test (IVPT) results of acyclovir from the test and RLD formulations. The test formulation was found to be qualitatively (Q1) and quantitatively (Q2) the same as the approved RLD. However, in the original submission, the data submitted were found inadequate due to deficiencies in method development, method validation, sample analysis and pivotal study for both IVRT and IVPT studies[2].

In the amendment dated 08/24/2017, the applicant responded to the above deficiencies. In the amendment BE review[1], the applicant's responses to the deficiencies related to the IVRT study were found acceptable. However, the applicant's responses to the deficiencies related to the IVPT study were found inadequate. The applicant's IVPT study is **inadequate** due to deficiencies in the IVPT method development, method validation, LC-MS/MS sample analysis and pivotal study.

The Division of Chemistry has completed its review of the physicochemical characterization data submitted and found it acceptable[3]. Therefore, the test formulation is deemed as Q1/Q2/Q3 (physiochemical characterization) the same as the RLD.

In the amendment of 04/05/2018 (unsolicited), the applicant submitted a multicenter *in-vivo* clinical endpoint study comparing Perrigo's Acyclovir Cream, 5%, to Valeant's Zovirax® Cream, 5%, which was recently reviewed by OGD/OB/Division of Clinical Review (DCR). In the review, DCR concludes as follows[4]:

> *DCR recommends approval of this application. Despite insufficient assay sensitivity to definitively demonstrate BE on its own, the overall results of Study PRG-NY-14-008, including comparable clinical response between the test and the reference product and no safety concerns, are adequate to provide the biorelevant information ordinarily provided by the in vitro permeation data (IVPT). Thus, Study PRG-NY-14-008 can support the available acceptable data for the in vitro BE approach for the proposed*

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[1] GDRP document: ANDA-208702-ORIG-1-AMEND-6, A208702N000DB-Review03-Amend08242017.pdf
http://panorama.fda.gov/document/view?ID=5b339d4d00756de7f913d61d490ff574
[2] GDRP document: ANDA-208702-ORIG-1, A208702N000DB_N01072016.docx
[3] GDRP document: ANDA-208702-ORIG-1, ANDA20870200000QTY.pdf
http://panorama.fda.gov/document/view?ID=58c9a8a801978b4b53547173717bd4be
[4] GDRP document: ANDA-208702-ORIG-1-AMEND-6, A208702N000DCR-Review.docx
http://panorama.fda.gov/task/view?ID=59a077b200c7af1f649709d663895295

formulation, which is Q1/Q2/Q3 the same to the RLD with acceptable in vitro release testing (IVRT) data. Therefore, based on the totality of information in the application, DCR concludes the proposed generic would likely be therapeutically equivalent to and substitutable for the RLD.

On 01/23/2019, DCR called a meeting to discuss the status of ANDA 208702 Amendment-6 and a regulatory path forward, with Division of Bioequivalence (DB) II and Dr. Sam Raney from OGD/ORS/Division of Therapeutic Performance (DTP)[5]. Based on this meeting and considering the facts that the proposed test formulation is Q1/Q2/Q3 the same as the RLD with an acceptable IVRT study, DBII has decided to defer to DCR on the determindation of BE of this product based on DCR's review on the in vivo clinical endpoint study data submitted by the applicant. In vivo clinical endpoint study can be considered as an alternative to the IVPT study as IVPT is used as a biorelevant test to support BE. Please note that the IVPT study data submitted in this application remain inadequate with deficiencies as noted above. Since DCR recommended the approval of this ANDA based on the totality of information and collective weight of evidence in the application, it has been decided not to communicate the deficiencies identified in the IVPT study to the applicant. Please see the meeting minutes for details[5].

[5] GDRP document: ANDA-208702-ORIG-1-AMEND-6, ANDA 208702 A 6 Acyclovir Cream 5% minutes Final.docx, dated 01/28/2019
http://panorama.fda.gov/document/preview?versionID=5c4f5b5f000990e65af3f20541a1cc5c&ID=5c4f5b5f000990e5a1a88d681fea1e61

BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA:	208702
APPLICANT:	Perrigo UK FINCO Limited Partnership
DRUG PRODUCT:	Acyclovir Cream, 5%

The Division of Bioequivalence II (DBII) 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 additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R. Ph.
Director
Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

2 COMPLETED ASSIGNMENT FOR 208702 ID: 37812

Reviewer: Li, Li **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Acyclovir Cream 5%

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
37812	8/24/2017	BIO	Addendum [1]	1	1
37812	8/24/2017	Parallel	Addendum (not for Clarification or Error Correction) [1]	1	1
				Total:	2

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	208702	
Drug Product Name	Acyclovir Cream	
Strength(s)	5%	
Applicant Name	Perrigo UK Finco Ltd Partnership	
Applicant Address	Wrafton, Braunton Devon, EX33 2DL UK	
US Contact Name and US Mailing Address	Maureen Rath, Sr. Manager, Regulatory Affairs Paddock Laboratories, LLC, a Perrigo Company 3940 Quebec Avenue North Minneapolis, MN 55427 regulatoryaffairs.usa@perrigo.com	
US Contact Telephone Number	(763) 732-0235	
US Contact Fax Number	(763) 732-0509	
Original Submission Date(s)	1/7/2016	
Submission Date(s) of Amendment(s) Under Review	08/24/2017	
Primary Reviewer	Li Li, Ph.D.	
Secondary Reviewer	Anil K. Nair, Ph.D.	
Tertiary Reviewer	N/A	
Study Number(s)	R&D Document :#68024	PER-AR-005-15-R00
Study Type(s)	In Vitro Drug Release Test	In Vitro Skin Permeation Test
Strength(s)	5%	5%
Analytical Site	Perrigo Israel Pharmaceuticals Ltd.	(b) (4)
Analytical Site Address	1 Zvi Bornstein St., Industrial Zone, Yeruham 8050315, Israel	
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☒ **Complete**

Waiver	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A		
Deficiency Classification	☒ Major ☐ Minor/IR ☐ N/A (Review is Adequate)		
Major Deficiency Theme	The applicant needs to repeat the IVPT study		
Justification for Major Designation	Review of the applicant's new IVPT study requires substantial expenditure of FDA resources		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: December 2016 RLD Number: NDA 021478 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO This review follows the revised/new guidance (December 2016)		
Communication	☐ ECD ☐ IR ☒ Not Applicable (Complete Response will be sent)		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	Formulation (Q1/Q2)	5%	☒ Adequate ☐ Inadequate
1, 4	In Vitro Drug Release Test	5%	☒ Adequate ☐ Inadequate
1	In Vitro Skin Permeation Test	5%	☐ Adequate ☒ Inadequate
1	Physicochemical Characterization (Q3)	5%	☒ Adequate ☐ Inadequate (based on drug quality review[1])

1 EXECUTIVE SUMMARY

This is a review of study amendment dated 08/24/2017 (for the review of *in vitro* option only).

The applicant has submitted the results of *In Vitro* Release Test (IVRT) and In Vitro Skin Permeation Test (IVPT) comparing a test product, Perrigo UK Finco Ltd Partnership's Acyclovir, 5% to the corresponding reference product VIB's Zovirax (acyclovir) Cream, 5% (NDA 021478).

The recently revised product-specific Draft Guidance for Acyclovir Cream, 5%, recommends an in vitro or in vivo option to determine bioequivalence (BE) between test and RLD product (posted the revised guidance in December 2016). The review of *in vitro* option to determine BE for current ANDA is based on the revised guidance.

In the original submission in January 2016, Perrigo requested a waiver of *in vivo* BE study for Acyclovir Cream, 5%. To support its request, the applicant submitted the following information: 1) test product formulation; 2) comparative physicochemical characterization of the test and RLD formulations; 3) comparative *in vitro* drug release test (IVRT) of acyclovir from the test and RLD formulations and 4) comparative IVPT results of acyclovir from the test and RLD formulations. However, in the original submission, the data submitted were found inadequate due to deficiencies in method development, method validation, sample analysis and pivotal study for both IVRT and IVPT studies.

In the current amendment dated 08/24/2017, the applicant responded to the above deficiencies. The reviewer finds that the applicant's responses to the deficiencies related to the IVRT study acceptable. On 03/21/2018, the DBII requested a non-clinical consult to the Division of Therapeutic Performance (DTP) on specific review-related questions about IVPT study for current ANDA. The DTP submitted its consult response on 05/17/2018. Based on the BE reviewer's assessment and the DTP consult response, the reviewer finds that the applicant's responses to the deficiencies related to the IVPT study are inadequate. The applicant's IVPT study is **inadequate** due to deficiencies in the IVPT method development, method validation, LC-MS/MS sample analysis and pivotal study (please see the details in Section 3.2.2.2 of this review).

The Division of Chemistry has completed its review of the physicochemical characterization data submitted and found it acceptable[1].

The Office of Study Integrity and Surveillance (OSIS) status for the current IVRT study (study #68024) site at Perrigo Company, Parsippany, NJ, is adequate. The OSIS status for the current IVPT study #PER-005-15-R00 is incomplete. As discussed in previous BE review, it is unclear whether the IVPT study site, (b) (4) retained the reserve samples for the current IVPT study. As we are asking the applicant to repeat the IVPT study in the current review, we will not request the applicant to clarify the reserve sample issue for the current IVPT study. Instead, we will remind the applicant to retain reserve samples for the future IVPT studies.

It is noted that in the recent amendment of 04/05/2018, Perrigo also submitted a Multicenter *In-vivo* clinical endpoint study comparing Perrigo's Acyclovir Cream, 5%, to Valeant's Zovirax®

[1] GDRP document: ANDA-208702-ORIG-1, ANDA20870200000QTY.pdf
http://panorama.fda.gov/document/view?ID=58c9a8a801978b4b53547173717bd4be

Cream, 5%, which is currently under review by OGD/OB/Division of Clinical Review (DCR). Please note that the current Amendment review focuses on *In Vitro* option only.

The application is **inadequate** with deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Acyclovir Cream, 5%
Reference Product	Zovirax® (acyclovir) Cream, 5%
RLD Manufacturer	Valeant International Bermuda (VIB)
NDA No.	021478
RLD Approval Date	12/30/2002

3.2 Review of Amendment (SD-6, dated 8/24/2017)

3.2.1 Deficiency Comment[2]

In December 2016, the Agency posted revised draft guidance on this drug product. This revised draft guidance provides updated product-specific recommendations for establishing bioequivalence (BE) to Zovirax® (acyclovir) Cream (NDA 021478). Please refer, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428195.pdf, for details on *in-vitro* options to compare your test product, Acyclovir Cream, 5 % w/w, to the corresponding reference listed drug (RLD) product, Zovirax® (acyclovir) Cream, 5 % w/w.

In Vitro Release Test (IVRT) Study

Method Development and Validation:

1. Please submit detailed method development procedures and report for IVRT method including all supportive data as it relates to the method development of the IVRT per the current guidance for this drug product. The report should include but is not limited to:

    a. Explanation for the choice of amount of sample used
    b. Explanation for the choice of receptor medium. Please submit supporting data, such as report #63767 as you mentioned in your IVRT method development report #66310-v1
    c. Explanation for the choice of sampling times, stirring rate
    d. Evaluation of membrane inertness
    e. Your IVRT method development report #66310 lacks details and supporting data. Please submit detailed method development report.

2. Please provide IVRT method validation data for the following parameters per the revised guidance for this drug product:

    a. IVRT Linearity and range
    b. IVRT Recovery, mass balance and dose depletion
    c. IVRT method discrimination sensitivity, specificity and selectivity
    d. IVRT Method robustness

[2] GDRP document: ANDA-208702-ORIG-1, Bioequivalence Review: A208702N000DB_N01072016.docx http://panorama.fda.gov/document/view?ID=57b1cabe0086038e6c14c97dd7f43375

3. You submitted method precision and inter-analyst intermediate precision data, but did not use the appropriate approach. Please evaluate the method precision and reproducibility following the current BE guidance for this drug product.

Pre-Study Analytical Method Validation

4. Your pre-study bioanalytical (HPLC) method validation report did not include limit of detection (LOD) and robustness for your analytical method. Please submit this information.

5. The acyclovir stability should be evaluated under the highest relevant temperature in the receptor solution for the duration of the IVRT study. Please submit the stability assessment data following the revised BE guidance.

Pivotal IVRT Study

6. You conducted sample analysis based on single point external standard method. It is noted that the acyclovir concentrations in the receiving media ranged from (b) (4) µg/mL which is not a narrow range. Please use validated multiple point calibration standards and quality control samples for quantitation of acyclovir in the IVRT samples.

7. You conducted the in vitro release tests using the Franz Diffusion Cell apparatus. However you did not provide details on how the test was conducted and what parameters were used. For example, it is not clear if (b) (4) (b) (4) Please submit a detailed systematic procedure and report of the setup and operation of the Vertical (Franz) Diffusion Cell and about the parameters 1, 2 and 3 requested above.

8. Please submit raw data for the IVRT testing in electronic SAS Transport format.

In Vitro Permeation Test (IVPT) Study

Method Development and Validation

9. You have submitted an IVPT method development report. However, your method development is not acceptably comprehensive to cover all the key aspects of the method. Please provide the following additional IVPT method development information as suggested in the current guidance:

   a. Explanation of study apparatus related parameters, *e.g.* (1) the choice of receptor chamber stirring rate, (2) rationale for having the epidermal chamber (b) (4) IVPT study (b) (4), and (3) the skin surface temperature measurement/control.

   b. Please provide details on the initial IVPT testing procedures and results, and explain (1) what are the blank and placebo samples used in the initial IVPT testing, whether skin samples were used in the blank and placebo samples, (2) for the linearity results, on page

7 of the submitted Method development report #PER-AR-006-15-R00, why the SPE method gave significantly higher response for STD1/2 to STD10 than the neat curve and PPT method.

c. Please justify the acceptance criteria of electrical resistance value of (b) (4) the reading of the diffusion medium, for the skin integrity test.

d. Please justify the choice of receptor medium and provide solubility data of acyclovir in the selected receptor medium. (b) (4) (b) (4)

e. Per the current guidance, the sampling time points and duration should be justified based on a pilot study. The duration of an IVPT study should be sufficient to characterize the majority of the dermal pharmacokinetic profile, or at least a sufficient amount of the flux profile to identify the maximum flux and a decline in the flux thereafter across subsequent time points.

f. The dose utilized in the IVPT study should be justified. Different dose amounts may be compared to evaluate the IVPT method.

g. Your pilot IVPT study only included skin samples from one donor. The current guidance recommends that a pilot IVPT study should have a minimum of 4 replicate skin sections per donor from multiple donors to support the development of appropriate conditions for the pivotal IVPT study.

10. (b) (4) (b) (4) Per the current guidance, skin from donors with significant background levels of acyclovir or other compounds that may interfere with the quantitation of acyclovir in receptor solution samples should be excluded from the study. Please explain your inclusion and exclusion criteria for choice of skin samples.

11. Please provide IVPT method validation data for the following parameters per the revised guidance for this drug product:

    a. IVPT precision and reproducibility
    b. IVPT Recovery, mass balance and dose depletion
    c. IVPT discrimination, sensitivity and selectivity
    d. IVPT Method robustness

12. Please validate the IVPT method for the study apparatus, methodologies and study conditions per the current BE guidance for this drug product.

Pre-Study Analytical Method Validation

13. Your analytical method validation report (PER-AR-004-15-R00) was mostly conducted using neat standard solutions only, which is not acceptable relating to the matrices relevant to the IVPT study. The sample analysis procedures should be validated in a manner comparable with the current FDA Guidance for Industry on Bioanalytical Method Validation and/or the ICH Harmonized Tripartite Guideline on Validation of Analytical Procedures Q2 (R1). Parameters to be validated include, but are not necessarily limited to, the following:

    a. Specificity, Selectivity, and Identification
    b. Linearity and Range
    c. Accuracy and Precision
    d. Sensitivity (Detection Limit and Quantitation Limit)
    e. Robustness
    f. Stability
    g. Recovery

Pivotal IVPT study

14. Study protocol should include inclusion and exclusion criteria for skin donor selection.

15. It is noted that multiple skin sections failed to meet your skin integrity test criteria (b) (4) (b) (4) (b) (4) Please explain why the skin sections that failed the skin integrity test criteria were still used for the IVPT test. It is also noted that the flux values for Donor 2 are higher than Donor 1 and 3.

.

16. The following information should be provided for the skin samples, (1) skin thickness for each skin section; (2) skin donor demographics (age, gender, and race); (3) skin storage information; (4) if skin sections from each donor were randomized to each treatment group.

17. Please ensure that your pivotal IVPT study is adequately powered.

18. You submitted two sets of total mass balance recovery and distribution data for test and reference products in the raw excel data sheet, one titled as "% distribution for 3 donors mean", and the other as "%distribution for 18 vessels". It is noted that the results table and graphs in these two Excel data sheets were not consistent. Please explain this discrepancy.

19. We could not locate information on randomly selected and retained the reserve samples for both test and reference products used in your pivotal IVPT study #PER-005-15-R00. Based on 21 CFR 320.38 and 320.63, samples should be retained and stored at study sites, or at independent third parties. Please clarify if you retained reserve samples of test and reference products for the IVPT studies. Please note that studies without retaining reserve samples will not be acceptable.

3.2.2 Applicant's Response and Reviewer's comment

3.2.2.1 In Vitro Drug Release Test (IVRT)

3.2.2.1.1 Method Development and Validation

Deficiency #1

FDA Comment #1

Please submit detailed method development procedures and report for IVRT method including all supportive data as it relates to the method development of the IVRT per the current guidance for this drug product. The report should include but is not limited to:

a. Explanation for the choice of amount of sample used
b. Explanation for the choice of receptor medium. Please submit supporting data, such as report #63767 as you mentioned in your IVRT method development report #66310-v1.
c. Explanation for the choice of sampling times, stirring rate
d. Evaluation of membrane inertness
e. Your IVRT method development report #66310 lacks details and supporting data. Please submit detailed method development report.

Perrigo Response #1

The IVRT Method Development report, submitted in the original application, has been revised to include:

a. An explanation for the choice of amount of sample used, see section 3.1 in report #66310-v2.
b. An explanation and all supporting data for the choice of receptor medium used, see section 2.1 in report #66310-v2.
c. An explanation for the choice of sampling times and stirring rate used, see section 3.5 and section 3.4 in report #66310-v2, respectively.
d. Evaluation of membrane inertness, see section 2.2.3 in report #66310-v2.
e. Full details and supporting data for the method development report.

Reviewer's Comment:

Choice of amount of samples

- The applicant submitted revised IVRT method development report in Module 5.3.1.4 of Amendment dated 8/24/17.
- (b) (4)

Choice of receptor medium

(b) (4)

Choice of sampling times and stirring rate

- The applicant stated that the choice of stirring rate (600 rpm) is based as recommended in 1724-Semisolid Drug Products Performance Tests. At this speed proper linearity and precision are obtained. The stirring rate used for the IVRT study is acceptable.
- The applicant also stated that the receptor phase sampling times (0.5, 1, 2, 4 and 6 hours) over 6 hours provide a robust linear range to assess transmission rates. (b) (4) (b) (4) This is acceptable.

Overall, the applicant's response to deficiency #1 is acceptable.

Deficiency #2

FDA Comment #2

Please provide IVRT method validation data for the following parameters per the revised guidance for this drug product.

a. IVRT Linearity and range

b. IVRT Recovery, mass balance and dose depletion

c. IVRT method discrimination sensitivity, specificity and selectivity

d. IVRT robustness

Perrigo Response #2

IVRT method validation data in response to FDA Comments 2.a to 2.d are presented in R&D Report #70649 "*Supplement to Report # 68945 - Validation of In-Vitro Release Test and Method of Acyclovir Cream, 5% through Synthetic Membrane*", as follows:

a. IVRT Linearity and range - see section 2.4.

b. IVRT Recovery, mass balance and dose depletion - see section 2.6.

c. IVRT method discrimination sensitivity, specificity and selectivity - see section 2.7.

d. IVRT robustness - see section 2.8.

Reviewer's Comment:

- The applicant submitted a supplement report #70649 to the original method validation report #68945.

(b) (4)

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

Table 7: Dose Permeation and Mass Balance

(b) (4)

[redacted]

IVRT method sensitivity, specificity and selectivity

- The IVRT method sensitivity, specificity and selectivity was assessed by comparing the release rate with different concentrations of Acyclovir Cream (2.5%, 5% and 7.5%) on the same day. The average slopes for each formulation were provided as follows:

Table 8: Release Rates of Different Strengths of Acyclovir Cream

Batch	Slope Q(µg/cm^2/sqrt hours)	%Label claim
A18D067	(b) (4) [redacted]	
A18D057		
A18D068		

(b) (4)

[redacted]

Figure 1 - Relationship between the Formulation Concentration of Acyclovir Cream, 5% and IVRT Release Rate (slopes)

The above table and figures shows that the IVRT method is sensitive, specific and selective enough to differentiate different strengths of Acyclovir Cream.

IVRT Robustness

- The applicant conducted robustness studies by varying the receptor solution temperature, receptor solution pH, mixing speed, and sample amount. The results are as follows:

Table 9: IVRT Method Robustness: Receptor Phase Temperature 31°C to 33°C

Temperature Robustness			
	Slope		
Cell Number	Temp 31 °C	Temp 32 °C	Temp 33 °C
1	(b) (4)		
2			
3			
4			
5			
6			
Mean	176.50	179.92	199.47
RSD, %	5	5	5
Difference, % (Coefficient of Variation, %)	(b) (4)		

Table 10: Receptor Solution Robustness

RP Robustness			
	Slope		
Cell Number	(b) (4)		
1			
2			
3			
4			
5			
6			
Mean	174.02	179.92	158.59
RSD, %	10	5	9
Difference, % (Coefficient of Variation, %)	(b) (4)		

Table 11: Speed Robustness

Speed Robustness			
	Slope		
Cell Number	(b) (4)		
1			
2			
3			
4			
5			
6			
Mean	174.28	179.92	180.99
RSD, %	7	5	4
Difference, % (Coefficient of Variation, %)	(b) (4)		

Table 12: Sample Amount Robustness

Sample Amount Robustness			
	Slope		
Cell Number	(b) (4)		
1			
2			
3			
4			
5			
6			
Mean	184.25	179.92	180.73
RSD, %	10	5	9
Difference, % (Coefficient of Variation, %)	(b) (4)		

The applicant's robustness studies are acceptable.

Overall, the applicant's response to Deficiency #2 is acceptable.

Deficiency #3

FDA Comment #3

You submitted method precision and inter-analyst intermediate precision data, but did not use the appropriate approach. Please evaluate the method precision and reproducibility following the current BE guidance for this drug product

Perrigo Response #3

Method precision and reproducibility studies have been performed following the approach specified in the Draft BE Guidance for Acyclovir Cream 5% (Revised December 2016). The results are presented in R&D Document #70649, section 2.5. The results support the selection of the receptor solution and the membrane.

Reviewer's Comment:

IVRT Precision and Reproducibility

- (b) (4)
- [redacted]

- The applicant's method precision data are acceptable. Hence the applicant's response to Deficiency #3 is adequate.

3.2.2.1.2 Pre-Study Analytical Method Validation

Deficiency #4

FDA Comment #4

Your pre-study bioanalytical (HPLC) method validation report did not include the limit of detection (LOD) and robustness for your analytical method. Please submit this information.

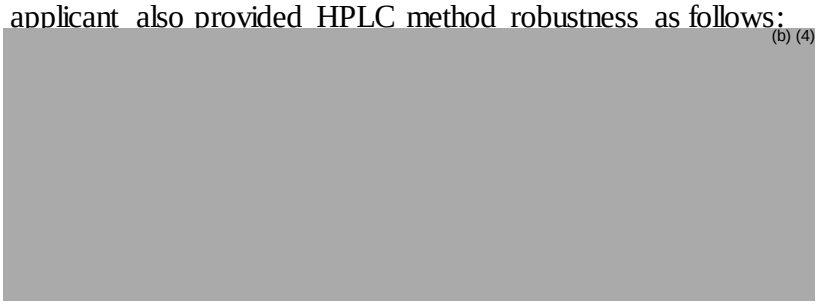
Perrigo Response #4

Perrigo's HPLC Method Validation Report has been revised (#68945-v2) to include a limit of .detection (LOD = 0.019329µg/mL) and robustness, see section 7.7 and section 7.8, respectively

Reviewer's Comment:

- The applicant provided the LOD as 0.019329 µg/mL for acyclovir.
- The applicant also provided HPLC method robustness as follows:

(b) (4)



- The applicant's response to Deficiency #4 is acceptable.

Deficiency #5

FDA Comment #5

The acyclovir stability should be evaluated under the highest relevant temperature in the receptor solution for the duration of the IVRT study. Please submit the stability assessment data following the revised BE guidance.

Perrigo Response #5

The acyclovir stability was evaluated under the highest relevant temperature in the receptor solution for the duration of the IVRT study (34ºC for 6 hours) in accordance with the recommendation of the Draft BE Guidance for Acyclovir Cream 5% (Revised December 2016), see section 2.3 in R&D Report #70649. The acyclovir was stable under these conditions. The acyclovir sample stability during storage for 14 hours at room temperature was also demonstrated as presented in section 7.6.2 of the HPLC Method Validation Report #68945.

Reviewer's Comment

- (b) (4)

- The applicant's response to Deficiency #5 is acceptable.

3.2.2.1.3 Pivotal IVRT Study

Deficiency #6

FDA Comment #6

You conducted sample analysis based on single point external standard method. It is noted that the acyclovir concentrations in the receiving media ranged from (b) (4) (b) (4) Please use validated multiple point calibration standards and quality control samples for quantitation of acyclovir in the IVRT samples.

Perrigo Response #6

(b) (4)

Reviewer's Comment

- [redacted] (b) (4)
- Reviewer considers applicant's response to Deficiency #6 is acceptable. Please note that similar issue has been discussed in more detail in BE amendment review for ANDA 205659[3].

Deficiency #7

FDA Comment #7

You conducted the in vitro release tests using the Franz Diffusion Cell apparatus. However you did not provide details on how the test was conducted and what parameters were used. For example, it is not clear if [redacted] (b) (4) [redacted] (b) (4) Please submit a detailed systematic procedure and report of the setup and operation of the Vertical (Franz) Diffusion Cell and about the parameters 1, 2 and 3 requested above.

Perrigo Response #7

The test procedure and parameters used were described in R&D Document #64719 "HPLC Method for In-Vitro Release Test of Acyclovir Cream, 5%", submitted in the original application.

[redacted] (b) (4)

Reviewer's Comment

[3] GDRP document: ANDA-205659-ORIG-1-Amend-9, A205659N000DB-Review01-Amend06262017.doc

- The applicant provided additional details for the IVRT method as follows:

(b) (4)

- The applicant's response to Deficiency #7 is acceptable.

Deficiency #8

FDA Comment #8

Please submit raw data for the IVRT testing in electronic SAS Transport format.

Perrigo Response #8

The raw data for the IVRT in electronic SAS Transport format is included in Dataset.

Reviewer's Comment:

The applicant's response to Deficiency #8 is adequate. We are actually using EXCEL spreadsheet not SAS to analyze IVRT data. Maybe we do not need to request SAS data in the future.

3.2.2.2 In Vitro Skin Permeation Test (IVPT)

3.2.2.2.1 In Vitro Skin Permeation Test (IVPT) Method Development and Validation

Deficiency #9

FDA Comment #9

You have submitted an IVPT method development report. However, your method development is not acceptably comprehensive to cover all the key aspects of the method. Please provide the following additional IVPT method development information as suggested in the current guidance:

a. (b) (4)

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BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 208702

APPLICANT: Perrigo UK FINCO Limited Partnership

DRUG PRODUCT: Acyclovir Cream, 5%

The Division of Bioequivalence II (DBII) has completed its review and has identified the following deficiencies:

In Vitro Permeation Test (IVPT) Study

Based on the IVPT data in your original submission, and your response to the bioequivalence (BE) deficiencies in the amendment dated August 24, 2017, DBII finds your IVPT study inadequate. Please adequately develop and validate your IVPT method, and repeat the pilot and pivotal IVPT studies following the detailed recommendations in the current draft product specific guidance (PSG) for this drug product. Please see the following suggestions and recommendations for your IVPT method development/validation, analytical method, pilot and pivotal studies.

IVPT Method Development and Validation

1. IVPT Method Development

   a) In the amendment dated 08/24/2017, (b) (4) (b) (4) The current PSG for Acyclovir Cream, 5%, recommends un-occlusion of the donor chamber during an IVPT study, because the occlusion of the cells would inhibit the drying and metamorphosis of the cream that would normally occur when used by patients, and as a result, any changes in the rate and extent of permeation associated with the metamorphosis of the test and reference products may be masked. (b) (4) (b) (4) (b) (4).

   b) According to your submission, the skin surface temperature was controlled (b) (4) (b) (4) (b) (4) (b) (4) The current PSG recommends measuring the temperature at the surface (*e.g.* using a calibrated infrared thermometer) to accurately characterize the control of the IVPT test system.

c) Per the PSG, the acyclovir stability should be assessed at the highest relevant temperature in the receptor solution that would be 32°C for 24 hours for the current study. Please provide this information.

d) [redacted] (b) (4)

e) Per your study report, a single dose of 5 mg cream/cm^2 was used for your IVPT study based on the Organization of Economic Cooperation and Development (OECD) guideline on the in vitro testing of skin absorption of chemicals. Although the selected dose of 5 mg cream/cm^2 is within the PSG recommended range of 5-15 mg cream/cm^2, there is no information provided to demonstrate that the specific study design and methodologies associated with your IVPT study are discriminating using the selected dose. Per the current PSG, a dose ranging study is recommended to make sure that the IVPT method is sensitive to potential differences in bioavailability between the Test and Reference products.

f) For the skin integrity test, you used an electrical impedance/conductance test, and set the acceptance criterion of electrical resistance [redacted] (b) (4). [redacted] (b) (4) (b) (4) [redacted] (b) (4) Please submit supporting data to substantiate that the cutoff value of 3 discriminates between normal and abnormal skin sections. Please also submit the information for the thickness of each skin section used for the IVPT study.

2. Pilot Study

Following the IVPT method development studies, a pilot IVPT study comparing the Test and Reference products is recommended, to estimate the number of donors required for the IVPT pivotal study. Per the current PSG, a pilot IVPT study performed with multiple skin donors and a minimum of 4 replicate skin sections per donor per treatment group is recommended. Your pilot study with one donor and 6 replicates using a single formulation is not appropriate to serve the purpose of a pilot study as recommended in the PSG. Please repeat the pilot study using the approach recommended in the PSG. Please note that the concentration of acyclovir in the skin and the mass balance of acyclovir based on concentration in the different layers of the skin is not qualitatively evaluated for establishing BE because it provides data only at one point in time, and does not support an adequate comparison of the pharmacokinetics (the rate) at which the acyclovir becomes available in the skin.

3. IVPT Method Validation

Your method validation using the pilot study data (with 1 donor, 6 replicates and a single formulation) is not acceptable. As stated above, a pilot study should be adequately powered. Please validate the IVPT method according to the recommendations in the PSG, in order to adequately develop, control, and validate an IVPT method. It is not sufficient to state that your method is similar to the method reported in the literature and therefore does not require validation. Results obtained from an IVPT method may be heavily dependent on the type of apparatus, skin, sampling technique, and how it is executed, hence it is critical that a method used for establishing BE is validated using exactly the same test system (same apparatus, dose amount and application technique, sampling time points and procedures, and other study parameters) as would be used for the pivotal IVPT BE study.

4. IVPT Analytical Method

a) (b) (4)

b)

c)

5. Pivotal Study

   a) Your pivotal IVPT study (3 donors, 6 skin samples per donor) is inadequate. Please repeat the pivotal IVPT study following the recommendations in the PSG.

   b) You stated that more than 40 donors would be needed to adequately power a pivotal IVPT study for establishing BE, and therefore such a study is not feasible. The estimate of 40 donors could be a consequence of having too few donors in the empirical dataset used to perform the calculations. Please ensure your repeat IVPT study is adequately powered.

Additionally, we note that, on 04/05/2018, you submitted a multicenter *In-vivo* clinical endpoint study comparing Perrigo UK Finco's Acyclovir Cream, 5%, (test product) to Valeant's Zovirax® Cream, 5% (reference product), which is currently under Agency's review.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R. Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4 OUTCOME

Completed Assignment for 208702 ID: 35588

Reviewer: Li, Li **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Acyclovir Cream 5%

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
35588	8/24/2017	BIO	ANDA Amendment [1]	1	1
35588	8/24/2017	BIO	Consult Review (For Consults to Other Office) [1]	1	1
35588	8/24/2018	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
35588	8/24/2017	Parallel	Study Amendment [1]	1	1
				Total:	4

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	208702	
Drug Product Name	Acyclovir Cream	
Strength(s)	5%	
Applicant Name	Perrigo UK Finco Ltd Partnership	
Applicant Address	Wrafton, Braunton Devon, EX33 2DL UK	
US Contact Name and US Mailing Address	Maureen Rath, Sr. Manager, Regulatory Affairs Paddock Laboratories, LLC, a Perrigo Company 3940 Quebec Avenue North Minneapolis, MN 55427 regulatoryaffairs.usa@perrigo.com	
US Contact Telephone Number	(763) 732-0235	
US Contact Fax Number	(763) 732-0509	
Original Submission Date(s)	1/7/2016	
Submission Date(s) of Amendment(s) Under Review	3/2/2016 and 06/01/2016 (Amended report and supporting data for IVRT study)	
Primary Reviewer	Li Li, Ph.D.	
Secondary Reviewer	Anil K. Nair, Ph.D.	
Tertiary Reviewer	Hongling Zhang, Ph.D.	
Study Number(s)	R&D Document :#68024	PER-AR-005-15-R00
Study Type(s)	In Vitro Drug Release Test	In Vitro Skin Permeation Test
Strength(s)	5%	5%
Analytical Site	Perrigo Israel Pharmaceuticals Ltd.	(b) (4)
Analytical Site Address	1 Zvi Bornstein St., Industrial Zone, Yeruham 8050315, Israel	
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☒ **Complete**

Waiver	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**		
Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**		
Overall Review Result	☐ **Adequate** ☒ **Inadequate**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO** **This review follows the revised/new guidance (December 2016)**		
Communication	☐ **ECD** ☐ **IR** ☒ **Not Applicable (Complete Response will be sent)**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	Formulation (Q1/Q2)	5%	☒ **Adequate** ☐ **Inadequate**
1, 4	In Vitro Drug Release Test	5%	☐ **Adequate** ☒ **Inadequate**
1	In Vitro Skin Permeation Test	5%	☐ **Adequate** ☒ **Inadequate**
1	Physicochemical Characterization (Q3)	5%	☐ **Adequate** ☒ **Inadequate** (based on drug quality review)

1 EXECUTIVE SUMMARY

This application contains the results of In Vitro Release Test (IVRT) and In Vitro Skin Permeation Test (IVPT) comparing a test product, Perrigo UK Finco Ltd Partnership's Acyclovir, 5% to the corresponding reference product VIB's Zovirax (acyclovir) Cream, 5% (NDA 021478).

The recently revised product-specific Draft Guidance for Acyclovir Cream, 5%, recommends an in vitro or in vivo option to determine bioequivalence (BE) between test and RLD product (posted the revised guidance in December 2016). The review of in vitro option to determine BE for current ANDA is based on the revised guidance.

Perrigo UK Finco Ltd Partnership requested a waiver of *in vivo* BE study for Acyclovir Cream, 5%. To support its request, the firm submitted the following information: 1) test product formulation; 2) comparative physicochemical characterization of the test and RLD formulations; 3) comparative *in vitro* drug release test (IVRT) of acyclovir from the test and RLD formulations and 4) comparative in vitro skin permeation test (IVPT) of acyclovir from the test and RLD formulations.

The test drug product contains the same active and inactive ingredients in the same concentration as the RLD product. Therefore it is deemed as qualitatively (Q1) and quantitatively (Q2) the same as the approved RLD. The firm's physicochemical characterization data have been reviewed by Office of Pharmaceutical Quality. The review results are deemed inadequate with deficiencies[1].

The firm submitted the IVRT study #60824 using the Franz diffusion cell apparatus (vertical for topical dosage forms). However, the IVRT study is **inadequate** due to deficiencies in the IVRT method development, method validation, and HPLC sample analysis (please see the details in Sections 3.4 and 3.6 of this review).

The applicant also submitted an IVPT study PER-AR-005-15-R00 using dermatomed human skin mounted onto static vertical Franz diffusion cells. The firm's IVPT study is **inadequate** due to deficiencies in IVPT method development, method validation, LC-MS/MS sample analysis and pivotal study (please see the details in Section 3.5).

Office of Study Integrity and Surveillance (OSIS) conducted an inspection from May 9-11, 2016 at Perrigo Company, Parsippany, NJ, auditing the IVRT study #68024 for the current ANDA 208702. The inspection outcome was classified as Official Action Indicated (OAI) and multiple observations were issued. Please see details in Section of 3.6 of this review for details. Overall,

[1] GDRP document: ANDA-208702-ORIG-1, Drug Product Quality Review, A208702 DS DP LBL R01

Reviewer concurs with the OSIS evaluation that firm's IVRT studies be partially acceptable for review due to the reserve sample issue.

For the IVPT study site at (b) (4) (b) (4) from the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within OSIS, DGDBE recommends accepting data for ANDA 208702 without an on-site inspection, as OSIS recently inspected this site and the inspectional outcome was classified as No Action Indicated (NAI). However, it is noted that OSIS inspection of the in vitro Bioequivalence (BE) studies conducted by (b) (4) revealed a reserve sample issue (Please see details in Section 3.6 of this review). At this time, it is unclear whether (b) (4) retained reserve samples for the current pivotal IVPT study. Considering all the above facts, the firm will be requested to clarify whether it retained reserve samples for the current IVPT study #PER-005-15-R00. If not, firm will be requested to re-conduct the IVPT studies.

The application is **inadequate** with deficiencies.

(b) (4)

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Acyclovir Cream, 5%
Reference Product	Zovirax® (acyclovir) Cream, 5%
RLD Manufacturer	Valeant International Bermuda (VIB)
NDA No.	021478
RLD Approval Date	12/30/2002

3.2 PK/PD Information

Most recent RLD label (provide embedded document)[3]	NDA021478label.pdf
Indication	ZOVIRAX Cream 5% is a herpes simplex virus (HSV) nucleoside analogue DNA polymerase inhibitor indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.
Boxed warning	N/A
Bioavailability	In a clinical pharmacology study which included 6 male volunteers, the cream was applied to an area of 710 cm^2 on the backs of the volunteers 5 times daily at intervals of 2 hours for a total of 4 days. Plasma concentration of acyclovir was assayed 1 hour after the final application which was below the limit of detection (0.01 μM) in 5 subjects and barely detectable (0.014 μM) in 1 subject. Systemic absorption of acyclovir from ZOVIRAX Cream is minimal in adults.
Food Effect	N/A
Tmax	Not available due to minimal systemic absorption
Metabolism	Acyclovir does not undergo metabolism in skin
Excretion	The average daily urinary excretion of acyclovir was approximately 0.04% of the daily applied dose.
Half-life	Not available due to minimal systemic absorption
Maximum Daily Dose	Apply five times a day

[3] Drugs@FDA Search "zovirax", NDA021478 label approved on 04/01/2014

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	http://www fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM428195.pdf (revised Dec 2016 Revised Draft Guidance on Acyclovir	
Summary of OGD or DB History	Approved ANDAs:	None
	Pending ANDAs:	(b) (4) [redacted]
	Controls:	There are many controls. The following are the few: 130527 (BE guidance development); 12-0482 (current ANDA), 12-0951, 12-0987, 13-0074 (formulation review); Please see Acyclovir Cream Review to support posting Draft guidance [4] for details.
	Protocols:	06-092, 08-048, 150012
	Pending Citizen Petitions and other legal and regulatory issues:	☐ Yes ☒ No

3.4 In Vitro Drug Release Test (IVRT)

3.4.1 In Vitro Drug Release Test (IVRT) Method Development[5]

The firm submitted the development report of in vitro release test for Acyclovir Cream 5% using vertical Franz diffusion cell. The IVRT method was optimized for the following parameters:

- **Receptor Medium Selection**

[4] GDRP document, , GDRP: 7482110 Review-Revision of Draft Guidance on Acyclovir Cream 5%.doc at: http://panorama.fda.gov/document/view?ID=5826b49b000c33a30af11a58dad8ef56

[5] DARRTS ANDA 208702 SD-1 dated 01/07/2016 Module 5.3.1.4 66310 Analytical Report

- According to firm's submission, the firm chose PBS 1:5 as the receiving medium based on previous knowledge, development report #63767. However, the firm did not submit report #63767.

- Reviewer checked how the firm prepared the selected receptor medium and the detail are as follows:
  - (b) (4)
  -
  -

- **Solubility of API in different receptor media:**

  - Acyclovir is soluble in diluted acids or bases, slightly soluble in water; insoluble in alcohol. Acyclovir solubility in the receptor medium 1:5 PBS at 32°C (b) (4)
  - Maximum acyclovir concentration achieved in in vitro test is (b) (4)
  - The solubility of acyclovir in the selected receptor medium (1:5 PBS buffer) is (b) (4) more than the maximum concentration of the drug obtained in the receiving medium after 6 hours of in vitro release testing.
  - This indicates that an optimal sink condition will be maintained throughout the course of the IVRT studies.

  Reviewer's comment:

  Firm chose to use 1:5 PBS as receptor medium for the IVRT assay based on previous knowledge and report #63767. As shown below, the solubility of acyclovir in the selected receptor solution is 28 times greater than the highest drug concentration in the receptor solution.

  As per the revised BE guidance for Acyclovir Cream 5%, the selection of the receptor medium should be justified. As the firm did not submit report #63767, it is unclear whether the selection of 1:5 PBS as receptor medium was adequately justified. Firm will be requested to provide report #63767 related to selection of receptor medium and will be informed that selection of receptor medium should be justified following the revised BE guidance for this drug product.

- **Membrane Selection**

  - **Membrane Binding**

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(b) (4)

Information Requested	
Bioanalytical method validation report location	Module 5.3.1.4
Study Report Number	R&D Document: #64719-v2
Analyte	Acyclovir
Method description	HPLC -UV
Limit of detection	NS
Limit of quantitation	0.045359 µg/mL, RSD 6%
System Suitability	Iniect standard solution into HPLC (b) (4)
Linearity and Range	R^2=1; Concentration range: 9.0717, 13.608, 18.143, 22.679, 34.019, 45.359, 68.038, 90.717, 113.40 and 136.08 µg/mL
Specificity	No interference no significant peak was observed at the retention time of acyclovir peak in the placebo sample, receptor phase, mobile phase and membrane after immersing in receptor phase.
Precision	System Precision: RSD 0.6%
Accuracy	105.8% to 107.0%.
Standard Stability	Standard solution: stable after 3 days at room temperature. Sample: stable for 14 hours at room temperature.
Robustness	NS

NS=not specified

Reviewer's Comment for Pre-Study Analytical Method Validation:

The firm submitted R&D Document #64719 which described HPLC method for in vitro release test of Acyclovir Cream 5%, and R&D Document #68945 for HPLC method validation report.

The firm did not submit validation on HPLC method limit of detection (LOD) and robustness.

The acyclovir stability should be evaluated under the highest relevant temperature in the receptor solution for the duration of the IVRT study. Firm will be recommended to assess the stability following the revised BE guidance.

The firm's pre-study analytical method validation is incomplete due to the above deficiencies.

3.4.4 In Vitro Drug Release Study Pivotal Study

3.4.4.1 In Vitro Drug Release Test (IVRT) Method

Study Information (IVRT)

Study Title	Comparative In-Vitro Release Test: Acyclovir from Acyclovir Cream, 5% Manufactured by Perrigo Israel Pharmaceuticals Ltd. versus Zovirax (Acyclovir cream, 5%) Manufactured by GlaxoSmithKline			
Study Type	In Vivo BE	**In Vitro BE**	Permeability	Other
Submission Location: **Study Report**	location: **5312-compar-ba-be-stud-rep\in-vitro-bio-68024**			
Validation Report	location: **5314-bioanalyt-analyt-met\in-vitro-bio-study-ivrt**			
Bioanalytical Report	location: **5314-bioanalyt-analyt-met\in-vitro-bio-study-ivrt**			
Clinical Site **(Name, Address, Phone #, Fax #)**	Perrigo Israel Pharmaceuticals Ltd., 1 Zvi Bornstein St., Industrial Zone, Yeruham 8050315, Israel Tel: +972-52-3667182 Fax: +972-8-6590619			
Principal Clinical Investigator **(Name, Email)**	Dr. Chalil Abu-Gnim, Senior Director Analytical R&D chalil.abu-gnim@perrigo.co.il			
Dosing Dates	March 19, 2014 – E3001 versus 070087 July 7, 2015 – A4001 versus 070087 July 6, 2015 – A4003 versus 070087 June 1, 2015 – 070087 versus 078607 June 2, 2015 – 070087 versus 078608			

Product Information for IVRT and IVPT

Product	**Test**	**Test**	**Test**	**Reference**	**Reference**	**Reference**
Product Name	Acyclovir Cream, 5%	Acyclovir Cream, 5%	Acyclovir Cream, 5%	Zovirax® (acyclovir) Cream, 5%	Zovirax® (acyclovir) Cream, 5%	Zovirax® (acyclovir) Cream, 5%

Manufacturer	Perrigo Israel	Perrigo Israel	Perrigo Israel	GSK[#]	GSK	GSK
Batch No.	078608*	070087	078607	A4001*	A4003	E3001
Manufacture Date	November 4, 2014	December 22, 2013	October 30, 2014	N/A	N/A	N/A
Expiration Date	N/A	N/A	N/A	01/17	01/17	05/16
Strength	5%	5%	5%	5%	5%	5%
Dosage Form	Cream	Cream	Cream	Cream	Cream	Cream
Bio-batch Size	(b) (4)			N/A	N/A	N/A
Production Batch Size				N/A	N/A	N/A
Potency	(b) (4)					
Content Uniformity (mean, % CV)	N/A	N/A	N/A	N/A	N/A	N/A
Dose and Treatment Period	N/A	N/A	N/A	N/A	N/A	N/A
Route of Administration	Topically	Topically	Topically	Topically	Topically	Topically

*These lots were used in the IVPT study; all lots were used in the IVRT study
[#]GSK=GlaxoSmithKline

Table. The following is a summary of the IVRT Method used in pivotal study

In Vitro Drug Release Testing (IVRT) Method	
IVRT Method SOP #	RN-RN-P-2001.03[7]
	Parameters
Number of cells examined	6
Cells Randomized (Y/N)	Y
Cells Occluded (Y/N)	Y
Number of Aliquots withdrawn	5
Type of Receptor Medium	Phosphate Buffer Saline (PBS) 1:5*
Type of Membrane	(b) (4)
Pre-soaking membrane time	Not specified
Diameter of membrane	(b) (4)
Stirring Rate	600 rpm
Temperature	32°C±1°C
Sampling times (hr)	0.5, 1, 2, 4, 6

[7] DARRTS ANDA 208702 SD-1 dated 01/07/2016 Module 2.7.1

	Diffusion Cell
Cell Type	(b) (4)
Cell Volume	7.0 mL
Dose	400 mg of Acyclovir Cream, 5%
Dosing Surface Area (cm^2)	(b) (4)

*PBS 1:5 is a fivefold diluted Phosphate Buffer Saline solution

The acyclovir samples were analyzed by HPLC as followings:

1. **Instrument Type** :
2. **Column** :
3. **Detection** :
4. **Column Oven Temperature** :
5. **Flow** :
6. **Injection Volume** :
7. **Run Time** :
8. **Mobile Phase** :
   Preparation of buffer :

(b) (4)

Sample Preparation

(b) (4)

Reviewer's Comment on in vitro release testing method

- The firm used vertical Franz diffusion cell apparatus as specified in the *Guidance for Industry*: SUPAC-SS.

- The firm randomized the test product and RLD in each run of the experiment.
- The firm's method lacks following details, if (1) [redacted]
- The firm will be requested to provide:
  - A detailed systematic procedure and report of the setup and operation of the Vertical (Franz) Diffusion Cell with details including information [redacted].

3.4.4.2 Within Study Analytical Report of In Vitro Drug Release Test Pivotal Study

Within Study Analytical Report Summary of Data Table

E3001 VS 070087	
Parameter	**Standard Sample**
Concentration (mcg/mL)	Only one standard with concentration of 58.262
Inter day Precision (%CV)	0.2

Parameter	**Quality Control Samples**				
Concentration (mcg/mL)	58.262	58.262	58.262	58.262	58.262
Inter day Accuracy (%Actual)	103.0	102.9	103.8	103.9	102.9

A4001 VS 070087	
Parameter	**Standard Sample**
Concentration (mcg/mL)	Only one standard with concentration of 55.772
Inter day Precision (%CV)	0.1

Parameter	**Quality Control Samples**				
Concentration (mcg/mL)	55.772	55.772	55.772	55.772	55.772
Inter day Accuracy (%Actual)	100.0	100.5	100.1	100.0	100.3

A4003 VS 070087	
Parameter	**Standard Sample**
Concentration (mcg/mL)	Only one standard with concentration of 55.772
Inter day Precision (%CV)	0.2

Parameter	Quality Control Samples				
Concentration (mcg/mL)	55.772	55.772	55.772	55.772	55.772
Inter day Accuracy (%Actual)	100.4	100.9	100.2	100.3	100.8

070087 VS 078607	
Parameter	Standard Sample
Concentration (mcg/mL)	Only one standard with concentration of 58.883
Inter day Precision (%CV)	0.3

Parameter	Quality Control Samples				
Concentration (mcg/mL)	58.883	58.883	58.883	58.883	58.883
Inter day Accuracy (%Actual)	100.1	100.9	101.4	101.3	100.6

070087 VS 078608	
Parameter	Standard Sample
Concentration (mcg/mL)	Only one standard with concentration of 58.883
Inter day Precision (%CV)	0.1

Parameter	Quality Control Samples				
Concentration (mcg/mL)	58.883	58.883	58.883	58.883	58.883
Inter day Accuracy (%Actual)	99.9	100.4	100.3	100.2	100.2

For complete in vitro release raw data in electronic excel format for the two batches see Section 5312-compar-ba-be-stud-rep\in-vitro-bio-68024.

Reviewer's comments:

- The firm conducted sample analysis based on single point external standard concentrations of 58.262, 55.772 or 58.883 µg/mL. These standard solutions are also used as QC samples in the run.

- Acyclovir concentrations in the receiving media ranged from (b) (4) µg/mL which is not narrow. Therefore, firm's single point external standard method is not acceptable. Firm will be recommended to use multiple point calibration standards and QC samples for quantitation analysis of in-vitro release testing.

HPLC analysis of IVRT samples is **inadequate**.

3.4.4.3 Data of In Vitro Drug Release Test

Was the following data submitted?			
Data from individual cells/vessels for Test/Reference	Yes		
Sample Chromatograms (20%)	Yes		
Analytical SOP(s)	Yes		
Location (volume and pages) of analytical SOP(s):	Module 5.3.1.4 66310 Section 64719 HPLC Method Analytical Report and Module 2.7.1 Section SOP for IVRT (page 83 of 92)		
Release Rate Comparison		**Comparison Results Comparison Limits: 75% to 133.33%**	
Stage One	**Firm**	Test (070087) vs.	RLD (A4001): (b) (4) %
			RLD (E3001): *
			RLD (A4003): %
		Test (070087) vs.	Test (078607):
			Test (078608):
	Reviewer	Verified firm's results by randomly checking firm's raw data and calculations	

*Please note that the IVRT data using RLD batch#3001are not considered for review here due to reserve sample issues.

- The followings are firm submitted In-Vitro Release Test data

  Comparative In Vitro Release Test of RLD # E3001 vs Test #070087

Table 1: Slopes and Ratio of Slopes of Comparative *In-Vitro* Release Test of Acyclovir from Acyclovir Cream, 5%, Lot #070087 and Zovirax Acyclovir Cream, 5%, Lot #E3001

(b) (4)

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(b) (4)

Reviewer's comment:

- Firm submitted raw data for the IVRT testing in Excel format only. The firm will be requested to submit raw data in electronic SAS Transport format.

- OSIS inspectional findings revealed that the IVRT testing site at Perrigo did not retain reserve samples for RLD batches E3001 and A4002, resulting in that the authenticity of the reference products for these two batches could not be verified. Therefore, the IVRT data using these two batches are not considered for review here. Please see Section 3.9 for details.

- The IVRT results for the stage one meet the acceptance limits of (b) (4) % for Test (batch #070087) *vs.* two different lots of Reference products (batch # A4001 and A4003) and two additional lots of Test products (Batch #078607 and 078608). The firm conducted acceptable comparative in vitro drug release rate tests of Acyclovir for the test and RLD formulations.

- It is noted that in the Cover Letter of Amendment dated 06/01/2016, firm stated that "following an FDA inspection on IVRT Bioequivalence Study No. 68024 submitted in ANDA 208702 Acyclovir Cream, 5%, Perrigo UK FINCO Limited Partnership (Perrigo) hereby submits the amended report and supporting data for Study No. 68024".

    - In the Amendment dated 06/01/2016, firm submitted additional IVRT studies conducted for Acyclovir Cream 5%, but not submitted in the original submission dated 01/07/2016.

Table 1: IVRT Studies Comparing RLD Batches to Test Product Batches #070087 and 078607

Study Date	Reference Batch /Expiry Date	Test Batch / Manufacturing Date
March 19, 2014 *	RLD E3001 / May, 2016	070087/ December, 2013
March 20, 2014	RLD F3002/ June, 2016	070087/ December, 2013
June 1, 2014	RLD E3001/ May, 2016	070087/ December, 2013
May 26, 2015	RLD H3003/ August, 2016	078607/ October, 2014
May 27, 2015	RLD L3004/ October, 2016	078607/ October, 2014
May 31, 2015	RLD F3002/ June, 2016	078607/ October, 2014
July 1, 2015	RLD A4002/ January, 2017	070087/ December, 2013
July 6, 2015 *	RLD A4003/ January, 2017	070087/ December, 2013
July 7, 2015 *	RLD A4001/ January, 2017	070087/ December, 2013

*Studies submitted in original ANDA #208702 for Acyclovir Cream, 5%.

Table 2: IVRT Studies Comparing Test Product Batches #070087 to #078607 and 078608

Study Date	Test Batch / Manufacturing Date	Test Batch / Manufacturing Date
June 1, 2015 *	070087/ December, 2013	078607/ October, 2014
June 2, 2015 *	070087/ December, 2013	078608/ November 2014

*Studies submitted in original ANDA # 208702 for Acyclovir Cream, 5%.

- The above two tables indicate that a total of nine (9) IVRT studies were conducted comparing seven (7) different lots of RLD products to two (2) lots of Test products (lots #070087 and 078607). Additionally, two IVRT studies were conducted comparing Test product lot#070087 to lots 078607 and 078608.
- Three (3) out of nine (9) IVRT studies were submitted in the original submission dated 01/07/2016, for RLD Lots #E3001, A4001 and A4003 *vs*. Test lot#070087.
- It is noted that three (3) out of nine (9) IVRT studies failed to meet the BE limit of criteria, which are for RLD lots H3003, F3002 and L3004 *vs.* Test lot#078607. All 3 failed studies were not submitted in the original submission.
- Reviewer compared the release rate and slope across all submitted 11 IVRT studies, 9 for Test vs. RLD, and 2 for Test vs. Test. Please see Section 4.5.2 for details. It is noted that for the 3 failed IVRT studies, RLDs showed higher release rate (slope) and the amount of drug released. Overall, a total of 13 sets of IVRT test results (9 Test results in 9 separate studies for Test vs. RLD, and 4 test results in two separate studies for Test vs. Test) on 3 different batches of Test products (Batches #070087, 078607 and 078608) were provided, and they all showed reasonably consistent results with slopes ranging from 129.26 to 172.38. In contrast, for 7 batches of RLD (Batches #E3001, F3002, H3003, L3004, A4001, A4002 and A4003) in 9 separate studies, the slopes range from 1 (b) (4). If excluding the three failed studies, the slopes for RLD range from 147.65-183.49 is comparable to the Test.
- For the failed IVRT studies, firm stated that investigations revealed that the failure could be attributed to phase separation and nonhomogeneous appearance of these batches of RLD (Batch #F3002, H3003 and L3004).

- (b) (4)

  - Please see Section 4.4.1 and 4.4.2 of this review for details regarding firm submitted additional IVRT studies and IVRT study comparison.
  - Based on all the facts stated above, reviewer agrees that the firm's reasoning is acceptable on the failed IVRT studies.

  The IVRT testing is **inadequate** due to deficiencies in IVRT method development, method validation and HPLC sample analysis.

3.5 In Vitro Skin Permeation Test (IVPT)

3.5.1 In Vitro Skin Permeation Test (IVPT) Method Development

The firm submitted method development report (#PER-AR-006-15-R00[8]) for the percutaneous absorption study of Acyclovir Cream (5%) formulation in human skin using modified Franz cell system. The method development involved two phases, the initial method condition and development and the suitability study in pilot study.

3.5.1.1 Initial method development

According to the ORS/DTP consult review on AND (b) (4) and the revised BE guidance for this drug product (revised Dec 2016)[10], an IVPT methodology and study design should consider the following parameters:

- **IVPT study apparatus**

  In the method development report, firm described following information on the diffusion cell system:

[8] DARRTS ANDA 208702 SD-1 dated 01/07/2016 Module 5.3.1.4 PER-AR-006-15-ROO-Acyclovir

(b) (4)

[10] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428195.pdf

- Static Franz Diffusion cell systems ([redacted])
- Receptor medium volume [redacted]
- Receptor compartment stirring speed ~600rpm
- Water jacket temperature controlled at 32.0±1°C
- The donor (epidermal) chamber [redacted]
- Ambient laboratory conditions. [redacted] for humidity and 21±4°C for temperature.

Reviewer's Comment:

- The firm did not justify the selection of receptor chamber stirring rate. The firm will be requested to provide justification for the selection of receptor chamber stirring rate.
- Firm will be recommended to monitor and control the skin surface temperature to be stable at 32.0±1°C (e.g. skin surface temperature can be measured by a calibrated infrared thermometer) for each individual cell prior to dosing.
- As per the revised BE guidance for this drug product (revised Dec 2016), the receptor chamber should be un-occluded for IVPT study.

- **IVPT skin and skin sample preparation**

Firm's IVPT method development report stated that:

- [redacted]

Reviewer's comment:

- Per the revised guidance, the skin thickness should be measured and reported for each skin section and should be relatively consistent for all donors whose skin is included in the study. Firm did not report the thickness for each skin section.
- The firm did not justify the acceptance criteria of electrical resistance value of [redacted] times the reading of the diffusion medium for the skin integrity test.

- **IVPT receptor solution**

According to the submitted protocol, firm

- Chose 1X Phosphate Buffered Saline (PBS) pH 7.4 as receptor medium.
- Selected PBS because PBS is the most commonly accepted medium for IVPT study.

- Did not provide acyclovir solubility in the receptor solution.

Reviewer's Comment

- The solubility and stability of acyclovir in the IVPT receptor medium should be provided, and the solubility should be high enough to maintain a sink condition.
- Per the current guidance, it is recommended to include an anti-microbial agent in the receptor medium if the study duration was longer than 24 hrs.

- **IVPT study dose**

According to the firm's protocol, approximate (b) (4) of Acyclovir cream was applied on skin sample surface area of (b) (4) which is equal to 5 mg/ cm^2.

(b) (4)

Reviewer's comment:

- Firm proposed dose amount 5 mg/ cm^2 is within the BE guidance recommended range of 5-15 mg/ cm^2.
- The firm did not provide justification (any clinical relevance to the dose selected) on how the dose of (b) (4) was selected. Though within the recommended range, firm still needs to provide justification on the dose selected for the IVPT study during method development, as per the revised guidance on this drug product

- **IVPT study drug permeation and receptor solution sampling**

Based on firm's method development report, initial study was as follows:
- Sample collections at 0 (pre-dose), 1, 2, 4, 6, 24, 30 and 48 hours.
- Sampling volume (b) (4) with replacement of fresh solution.
- Three pieces of skin from one donor were used for the initial IVPT method development and the results were as follows:

- [redacted] (b) (4)
- [redacted]

Reviewer's Overall Comment on Firm's IVPT Method Development

Overall, the firm has submitted IVPT method development report #PER-AR-006-15-R00, summary of Pilot study results, and IVPT method and procedure [redacted] (b) (4). However, the firm's IVPT method development is not acceptably comprehensive to cover all the key aspects of the method which are listed as follows:

- Related to Study Apparatus
    - The firm did not justify the selection of receptor chamber stirring rate.
    - The donor chamber should not be covered.
    - Firm will be recommended to monitor and control the skin surface temperature to be stable at 32.0±1°C (e.g. skin surface temperature can be measured by a calibrated infrared thermometer) for each individual cells prior to dosing.
- Related to Skin samples
    - The firm should justify the acceptance criteria of electrical resistance value 3 times the reading of the diffusion medium for the skin integrity test conducted on the skin prior to IVPT study.
    - Skin thickness should be measured and reported for each skin section and should be relatively consistent for all skin samples used.
    - Firm should provide details on skin used such as 1) donor demographics (age, gender, and race); 2) skin storage duration and temperature and the number of freeze-thaw cycles; 3) whether skin sections from each donor randomized to each treatment group.
    - Inclusion and exclusion criteria for skin samples should be included in the study protocol.
- Related to Receptor medium

- The firm should justify the selection of PBS as receptor medium, providing solubility and stability data of acyclovir in the selected receptor medium.
- The firm should justify the study duration and sampling times for the IVPT study. An anti-microbial agent in the receptor medium is recommended if the study duration is longer than 24 hrs.

- Per the current BE guidance, it is recommended to replace entire receptor solution at each sampling times to maintain optimal sink condition.

- Related to Study dose

  - The firm should provide justification on the dose selected for the IVPT study.
  - Per the revised guidance, different dose amounts may be compared to evaluate the IVPT method discrimination such as sensitivity and selectivity.

- Related to Initial IVPT method

  - Firm did not provide details on the initial testing procedures, *e.g.*, it is not clear what are blank and placebo samples, whether skin samples were used in the blank and placebo samples.
  - Firm did not explain the initial study results in detail, e.g. the linearity results table.

  The firm's method development is **inadequate.**

3.5.2 In Vitro Skin Permeation Test (IVPT) Method Validation

The firm submitted analytical method validation protocol (b) (4) and analytical method validation report #PER-AR-004-15-R00 for the IVPT study.

Reviewer's Overall Comment on the IVPT Method Validation

The firm has submitted analytical method study protocol and validation report for the IVPT study. However, the firm's method validation report #PER-AR-004-15-R00 is mostly related to the LC-MS/MS analytical method. The firm will be recommended to submit a comprehensive method validation report following the latest revised BE guidance.

The firm's pre-study method validation is **inadequate.**

3.5.3 Pre-Study Analytical (LC-MS-MS) Method Validation for IVPT study

Information Requested	Data
Bioanalytical method validation report location	DARRTS ANDA #208702 in Module 5.3.1.4, PER-AR-004-15-R00 Validation Report. Submission date: 01/07/2016
Study Report Number	PER-AR-004-15-R00

Analyte	Acyclovir
Internal standard (IS)	Acyclovir-d4
Method description	Solid Phase Extraction was used for sample extraction. UPLC-MS/MS was used for sample analysis.
System Suitability	Peak response ratio of six replicate solution injections NMT (b) (4)%
Specificity	Specificity of the method is demonstrated by analysis of the diffusion medium and the blank sample solution (collected at 24 hours after performing an IVPT testing of human skin without applying product). Acceptance criteria: • No significant interference peak from the diffusion medium at the RT of acyclovir. • No significant interference peak from the blank sample solution at the RT of acyclovir. The interference, if any, should be ≤30% of STD1. (b) (4) Failed to meet the specificity criteria provided in the validation protocol.
Limit of quantitation	LOD: 0.245 ng/mL; LOQ: 0.490 ng/mL (both LOD and LOQ used neat solution only)
% recovery (and %CV) at each concentration tested	(b) (4)
Average recovery of IS (%)	Not Reported
Standard curve concentrations (ng/mL)	**Curve 1**: 0.0979, 4.8950, 24.4750, 97.9000, 195.8000 and 391.6000 ng/mL **Curve 2**: 9.4580, 18.9160, 94.5810, 189.1620, 472.9050 and 945.8100 ng/mL **A new set of curve 2**: 10, 20, 100, 200, 500, 1000, 3000 and 5000 ng/mL
QC Intraday precision and accuracy range (%)	(b) (4)

	(b) (4)
QC Interday precision range (%)	See above table
QC Interday accuracy range (%)	See above table
Bench-top stability (hrs)	Standard and sample solutions: 2days at 2-8°C
Stock stability (days)	8 days at 2-8°C
Processed stability (hrs)	Standard and sample solutions (receptor solution, skin wash and skin strip samples): 2days at 2-8°C
Robustness	(b) (4)

	(b) (4)

Comments on the Pre-Study Method Validation: Inadequate (not acceptably comprehensive)

- Firm's analytical method validation report (PER-AR-004-15-R00) was mostly conducted using neat standard solutions only. The analytical method should be validated in a manner compatible with the current FDA Guidance for Industry on Bioanalytical Method Validation, and be relevant to the IVPT study. Parameters to be validated include, but are not necessarily limited to, the following:

    a. Specificity, Selectivity, and Identification
    b. Linearity and Range
    c. Accuracy and Precision
    d. Sensitivity (Detection Limit and Quantitation Limit)
    e. Robustness
    f. Stability
    g. Recovery

- Significant interferences at the RT of acyclovir were observed in the blank samples from IVPT study without drug product during the specificity study. According to the firm, interference probably came from endogenous substances in the skin. Since the amount of interference varied among the skin pieces, the firm stated that a consistent background subtraction was not possible. Firm noted that all validation results were evaluated with the interference.

  Acyclovir is a nucleoside analogue which share structural similarities with endogenous compounds. However, LC-MS/MS instrument offers high selectivity. The firm did not provide detailed explanation on the interference detected in the blank sample, for example, 1) how data analysis was conducted to justify that the interference probably was endogenous substance in donor skin; 2) whether all or only some donor skins contain this interference substance; 3) method development with various types of HPLC columns and conditions to improve method specificity.

  Per the revised guidance, skin from donors with significant background levels of acyclovir or other compounds that may interfere with the quantitation of acyclovir in receptor solution

samples should be excluded from the study. Hence, firm should explain its inclusion and exclusion criteria for skin sample selection.

Overall, firm's IVPT pre-study analytical (LC-MS/MS) method validation is inadequate.

3.5.4 In Vitro Skin Permeation Test Pivotal Study #PER-AR-005-15-R00

3.5.4.1 In Vitro Skin Permeation Test (IVPT) Pivotal study Method

Study Information (IVPT)

Study Title	Characterization of the Percutaneous Absorption of Acyclovir from Acyclovir Cream (USP 5% w/w) Formulations Dosed on Human Donor Skin Using the Finite Dose In Vitro Permeation Test Model			
Study Type	In Vivo BE	**In Vitro BE**	Permeability	Other
Submission Location: **Study Report**	location:**5312-compar-ba-be-stud-rep\per-ar-005-15-r00**			
Validation Report	location: **5314-bioanalyt-analyt-met\in-vitro-bio-study-ivpt**			
Bioanalytical Report	location: **5314-bioanalyt-analyt-met\in-vitro-bio-study-ivpt**			
[redacted] (b) (4)				

Product Information for IVPT

Product	Test	Reference
Product Name	Acyclovir Cream, 5%	Zovirax® (acyclovir) Cream, 5%
Manufacturer	Perrigo Israel	GlaxoSmithKline
Batch No.	078608	A4001
Manufacture Date	November 4, 2014	N/A
Expiration Date	N/A	01/17
Strength	5%	5%
Dosage Form	Cream	Cream
Bio-batch Size	[redacted] (b) (4)	N/A
Production Batch Size	[redacted]	N/A
Potency	104.1%	101.0%
Content Uniformity (mean, % CV)	N/A	N/A
Dose and Treatment Period	N/A	N/A
Route of Administration	Topically	Topically

Methods and procedures for IVPT study of Acyclovir Cream (5%) using Human Donor Skin

- **Franz Diffusion Cell System** [redacted]

Ring thickness:	3.2mm
Teflon ring diameter:	15mm
Franz cell diameter:	15mm
Surface area:	1.7671 cm^2
Diffusion medium:	PBS pH 7.4
Temperature (°C):	32°C±0.5°C
Stirring speed:	600 rpm
Medium volume:	12mL
Aliquot volume:	0.5mL, with medium replacement
Number of aliquots withdrawn:	7
Sampling time (hour):	0, 4, 8, 14, 17, 20, 24

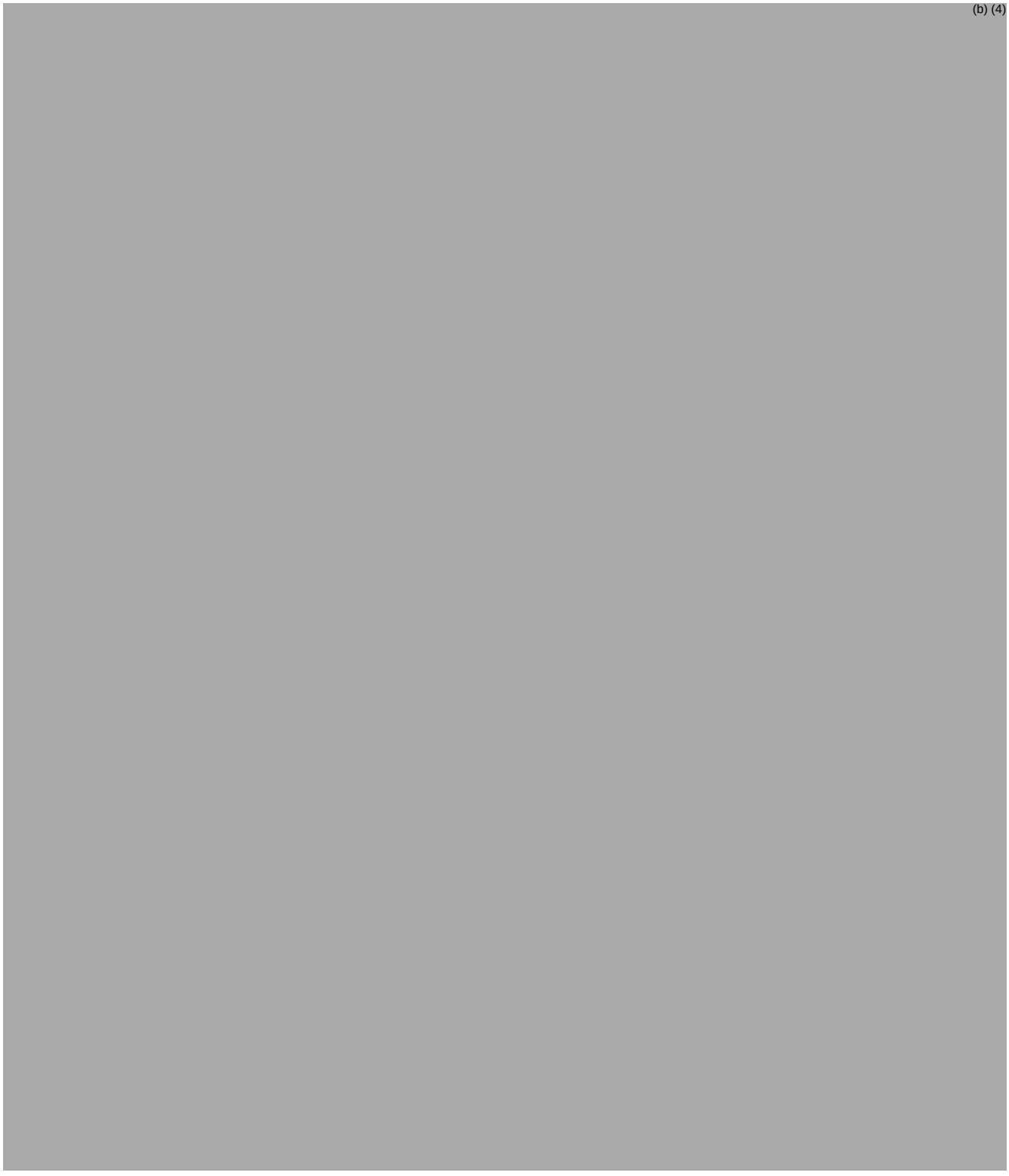
- **Chromatographic conditions**

Instrument:	[redacted]
UPLC Column:	
Column Temperature:	
Sample Temperature:	
Mobile phase:	
Injection volume:	
Flow rate:	
Run time:	

- **Procedures**

  - Human skin Preparation and Integrity Test
    - Thaw the skin to room temperature
    - Cut into small patch with diameter NLT [redacted] mm
    - Soak the skin patch in diffusion medium for at least 30min.
    - Perform skin integrity test using Precision LCR Meter
    - The obtained electrical resistance value of the skin should be at least 3 times greater than the reading of the diffusion medium

  - Preparation of IVPT samples (receptor medium samples, curve 1 samples)



- **Reviewer's comment on IVPT procedures**

  - The firm used vertical Franz cell for its IVPT studies which is acceptable for IVPT study.

- An aliquot of Receptor solution (0.5 mL) was sampled and replaced at 0, 4, 8, 12, 14, 17, 20 and 24 hour time points. Per the revised BE guidance for Acyclovir Cream, 5%, for IVPT study using a vertical diffusion cell, it is recommended that the entire receptor solution volume is removed and replaced at each time point to provide optimal sink conditions.
- (b) (4)
- PBS buffer pH 7.4 was used as receptor medium. However, the firm did not justify the selection of PBS buffer as receptor solution and did not provide the solubility and stability data of acyclovir in PBS buffer. The minimum solubility of acyclovir in the IVPT receptor solution should be empirically determined, and should be ideally by an order of magnitude. Per the revised guidance, the stability of acyclovir in the receptor solution samples should be validated.
- The receptor chamber was stirred at ~600 rpm. The firm did not justify how the stirring rate was optimized.
- (b) (4). Per the revised BE guidance, it is recommended that the dose should not be occluded, unless it is occluded in clinical use.
- According to the firm's method, approximate (b) (4) of Acyclovir cream was applied on each skin surface, which is equal to 5 mg/cm^2. The dose was evenly dispersed and gently rubbed into the surface of the skin. The dose of 5 mg/cm^2 is clinically relevant. Per the revised guidance, the firm should justify the dose utilized in the study, even when the dose is clinically relevant.

- A total of eight (8) sampling time (0, 4, 8, 12, 14, 17, 20 and 24 hour) points were used in the study. Per the revised BE guidance, the sampling frequency should be selected to provide suitable resolution for the flux profile, and a minimum of 8 non-zero sampling time points is recommended across the study duration (e.g. 48 hours).

Protocol Deviations (IVPT)

Study No. PER-AR-005-15-ROO
In the protocol, (b) (4) should have read (b) (4) without a version number since method was updated to RO I after the pilot study.
During the UPLC-MS/MS run for 0-14 hour IVPT samples, five instead of six injections were used in the system suitability calculation since one injection has no Acyclovir peak (reference: LNB-1 5-025, p.80).
% Distribution in different skin layers was expressed as % of total distribution according to method (b) (4) 1 rather than as % of applied dose as mentioned in in the protocol.

3.5.4.2 Data of In Vitro Skin Permeation Test (pivotal study)

The test and reference products were evaluated on 6 replicates of skin from each of the three donors, (b) (6). Each donor had one non-dosed control cell included as a blank. The test formulation, lot#078608 and reference product, lot#A4001 were dosed on skin sections from the same three donors on the same day.

- **Skin Integrity Test**

The electrical resistances of skin pieces were determined using a LCR meter at 32°C and the results are shown in the table below. The measured electrical resistance values of the skin tissue should be at least 3 times greater than the reading of the diffusion medium.

Summary of skin integrity test results

Vessel #	Skin electrical resistance (kΩ)					
	Donor 1		Donor 2		Donor 3	
	Test	Reference	Test	Reference	Test	Reference
1	2.3260	2.3890	1.9159	1.8053	3.7053	3.9946
2	2.9924	2.3911	1.7428	1.9230	4.2118	4.2870
3	3.3353	2.0363	1.4437	1.7377	4.1715	4.3284
4	3.3285	2.1708	1.6478	1.8796	3.8887	4.0629
5	1.8859	1.8834	1.7253	1.8061	3.3176	3.6976
6	2.1352	2.1632	1.5014	1.7661	4.7266	4.4869
Blank	2.4273		1.7236		4.2933	
Receptor medium 631.74Ω						

Reference: LNB-15-024, p.24.

Reviewer's Comments:

It is noted that multiple skin sections failed to meet the skin integrity test criteria [Donor 1 (Vessel #5 for both T and R) and Donor 2 (Vessel #1R, 2T; Vessels #3, 4, 5 and 6 for both T and R)]. According to firm's protocol, only skin with electrical resistance value of (b) (4) the reading of the diffusion medium can be used for the IVPT test. The firm will be requested to explain why skin sections that failed the skin integrity test criteria were still used for the study.

Per the revised BE guidance, the test parameters and acceptance criteria utilized for the skin barrier integrity test should be justified based upon relevant literature references or other information. The firm should provide this information.

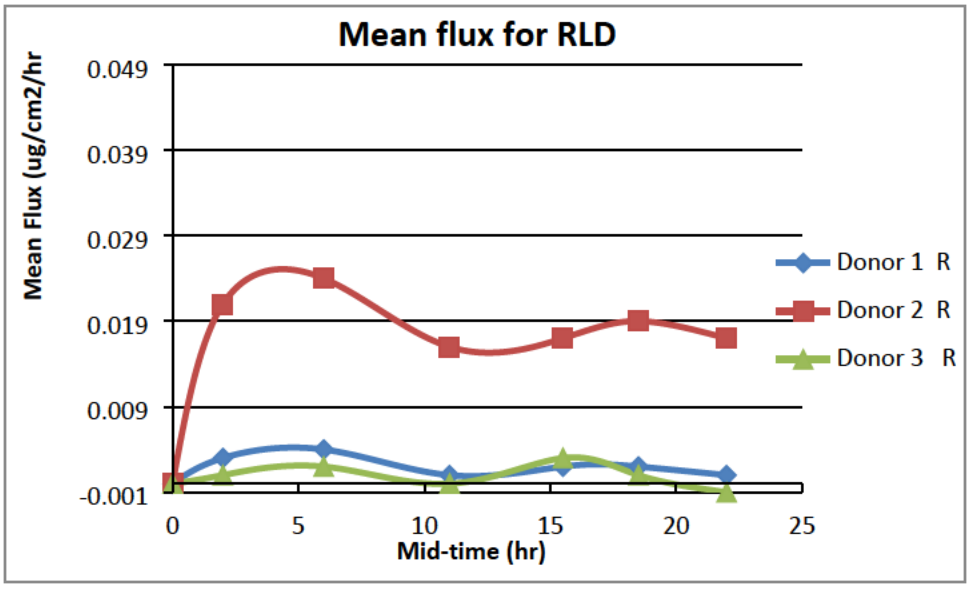
The firm did not provide details on skin samples such as 1) donor demographics (age, gender, and race); 2)skin storage duration and temperature and the number of freeze-thaw cycles 3) whether skin sections from each donor randomized to each treatment group or not.

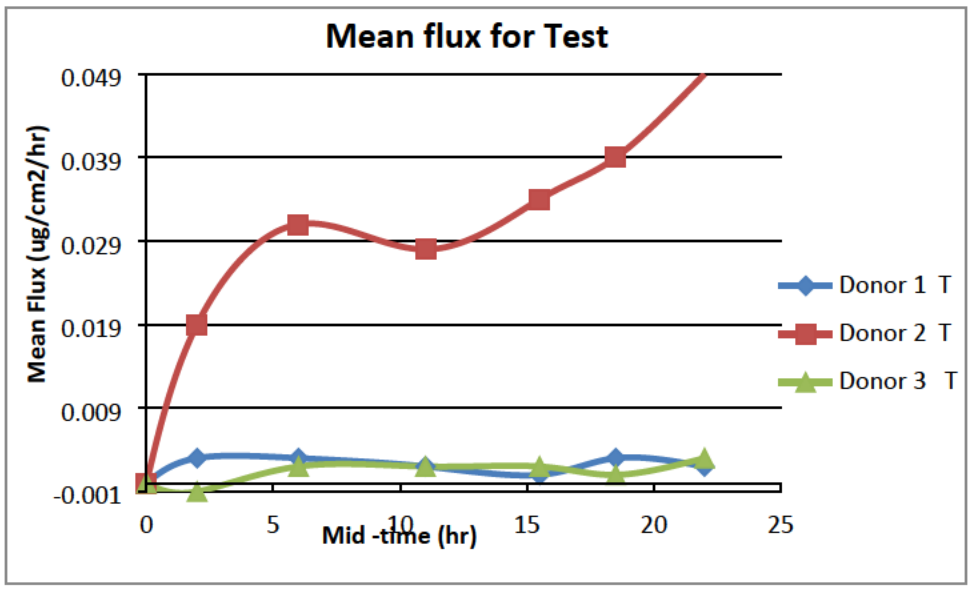
- **Skin Permeation**

The rate of penetration is presented as the flux. The results for percutaneous absorption (flux) are shown in the following tables and figures:

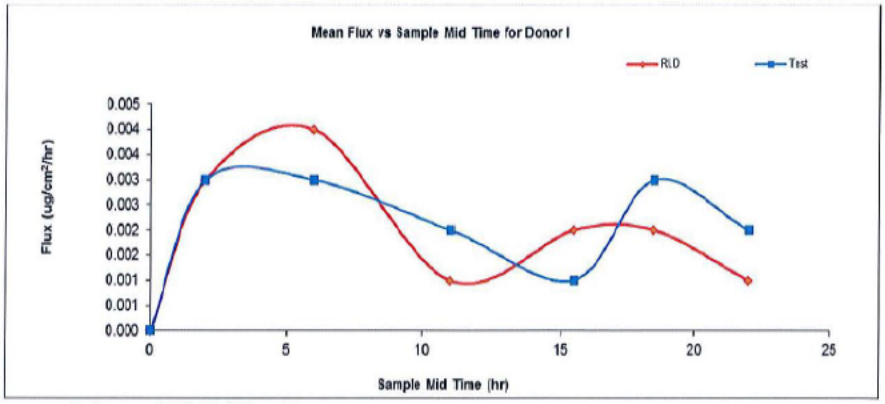
3 Donors Mean Flux for RLD							
Time (hour)			Lot# A4001				
			Mean Flux (µg/cm²/hr) : Across Donor				
Time Point	Sample Duration	Mid-Time	Donor 1	Donor 2	Donor 3	Mean	SD
hour	hour	hour	mean	mean	mean	(n=3)	(n=3)
0	0	0	0.000	0.000	0.000	0.000	0.000
4	4	2	0.003	0.021	0.001	0.008	0.011
8	4	6	0.004	0.024	0.002	0.010	0.012
14	6	11	0.001	0.016	0.000	0.006	0.009
17	3	15.5	0.002	0.017	0.003	0.007	0.008
20	3	18.5	0.002	0.019	0.001	0.007	0.010
24	4	22	0.001	0.017	-0.001	0.006	0.010

3 Donors Mean Flux for Test							
Time (Hour)			Lot#78608				
			Mean Flux (µg/cm²/hr) : Across Donor				
Time Point	Sample Duration	Mid-Time	Donor 1	Donor 2	Donor 3	Mean	SD
hour	hour	hour	mean	mean	mean	(n=3)	(n=3)
0	0	0	0.000	0.000	0.000	0.000	0.000
4	4	2	0.003	0.019	-0.001	0.007	0.011
8	4	6	0.003	0.031	0.002	0.012	0.016
14	6	11	0.002	0.028	0.002	0.011	0.015
17	3	15.5	0.001	0.034	0.002	0.012	0.019
20	3	18.5	0.003	0.039	0.001	0.014	0.021
24	4	22	0.002	0.049	0.003	0.018	0.027

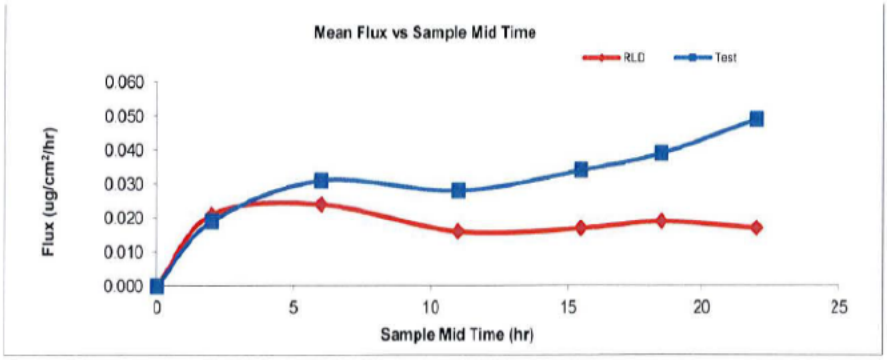




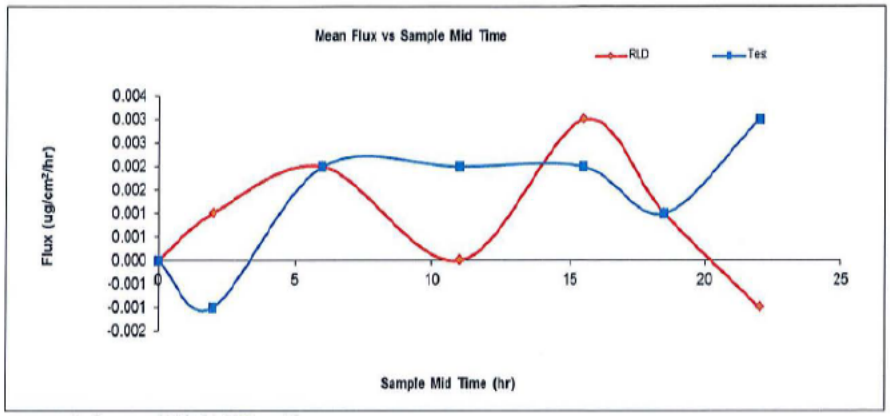
Flux vs. mid-time point from reference and test lots for donor1



Flux vs. mid-time point from reference and test lots for donor 2



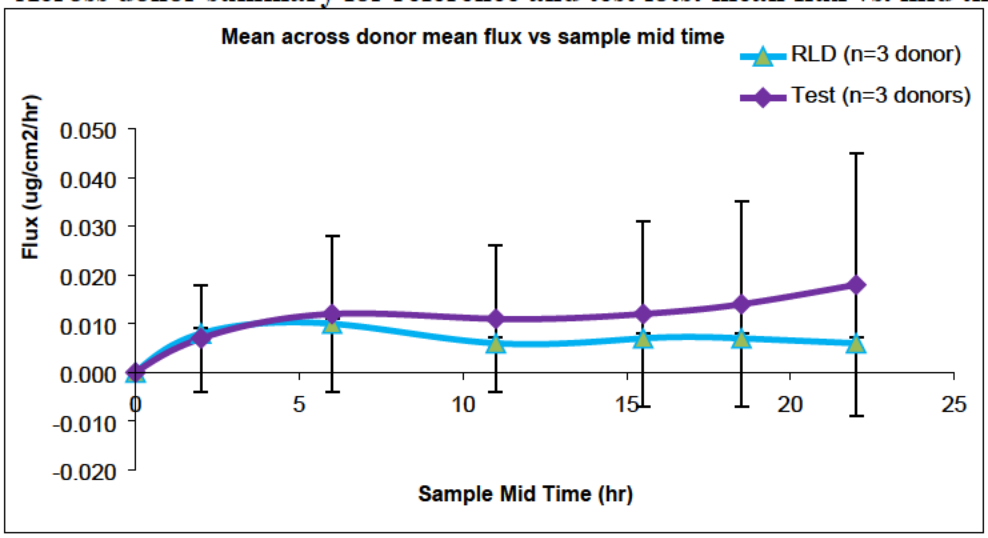
Flux vs. mid-time results from reference and test lots for donor 3



Across donor summary of Acyclovir mean flux from test and reference lots

Time (h)		Reference lot mean flux (µg/cm²/h) (across donor)	Test lot mean flux (µg/cm²/h) (across donor)
Time Point	Mid-Time		
0	0	0.000	0.000
4	2.0	0.008	0.007
8	6.0	0.010	0.012
14	11.0	0.006	0.011
17	15.5	0.007	0.012
20	18.5	0.007	0.014
24	22.0	0.006	0.018

Across donor summary for reference and test lots: mean flux vs. mid time point



- **Skin permeation data for individual cell**

<u>Donor 1</u>

Summary of flux results from test lot for donor 1

Time point h	Mid-time h	Flux (µg/cm²/h) test lot							
		T1	T2	T3	T4	T5	T6	Mean	SD
0	0	[redacted]					(b) (4)	0.000	(b) (4)
4	2.0							0.003	
8	6.0							0.003	
14	11.0							0.002	
17	15.5							0.001	
20	18.5							0.003	
24	22.0							0.002	

Summary of flux results from reference lot for donor 1

Time point h	Mid-time h	Flux (µg/cm²/h) reference lot							
		R1	R2	R3	R4	R5	R6	Mean	SD
0	0	[redacted]					(b) (4)	0.000	(b) (4)
4	2.0							0.003	
8	6.0							0.004	
14	11.0							0.001	
17	15.5							0.002	
20	18.5							0.002	
24	22.0							0.001	

Accumulated Release Amount (µg); RLD Lot# A4001 for Donor 1

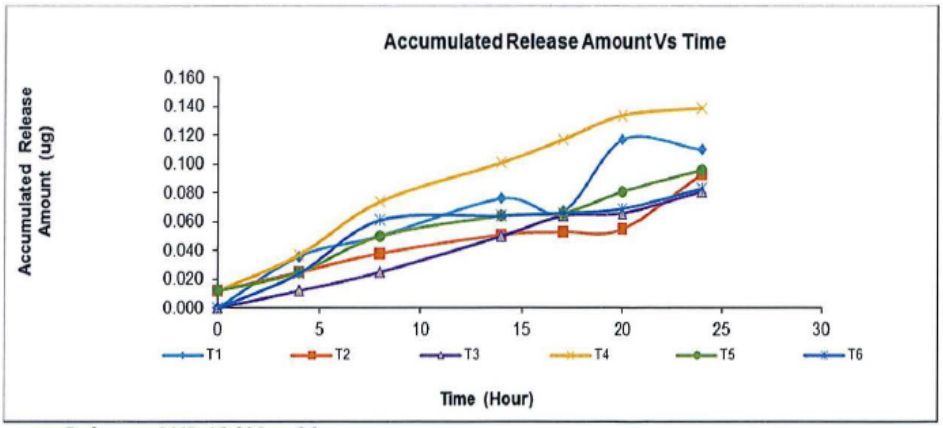
Time (hours)	G1 (Control*)	R1	R2	R3	R4	R5	R6	Mean
0	3208.476	[redacted]					(b) (4)	0.018
4	240.379							0.041
8	258.096							0.067
14	249.355							0.077
17	253.397							0.086
20	244.355							0.100
24	247.340							0.107

*Control: Non-dosed control as blank; These values are unusually high for a blank sample. Firm noted that these are unexpected high values observed for control, but did not provide explanation.

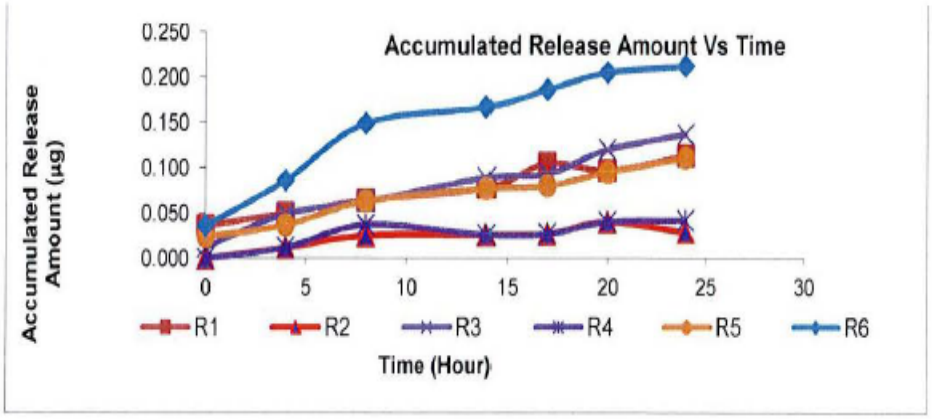
Accumulated Release Amount (µg); Test Lot# 78608 for Donor 1

Time (hours)	T1	T2	T3	T4	T5	T6	Mean
0	[redacted]					(b) (4)	0.006
4							0.027
8							0.050
14							0.068
17							0.072
20							0.087
24							0.100

Cumulative amount of Acyclovir versus time for donor 1 from test lot



Cumulative amount of Acyclovir versus time from reference lot for donor 1



Donor 2

Summary of flux results from test lot for donor 2

Time point h	Mid-time h	Flux (µg/cm²/h) test lot							
		T1	T2	T3	T4	T5	T6	Mean	SD
0	0	[redacted] (b) (4)						0.000	[redacted] (b) (4)
4	2.0							0.019	
8	6.0							0.031	
14	11.0							0.028	
17	15.5							0.034	
20	18.5							0.039	
24	22.0							0.049	

Summary of flux results from reference lot for donor 2

Time point h	Mid-time h	Flux (µg/cm²/h) reference lot							
		R1	R2	R3	R4	R5	R6	Mean	SD
0	0	[redacted] (b) (4)						0.000	[redacted] (b) (4)
4	2.0							0.021	
8	6.0							0.024	
14	11.0							0.016	
17	15.5							0.017	
20	18.5							0.019	
24	22.0							0.017	

Accumulated Release Amount (µg); RLD Lot# A4001 for Donor 2

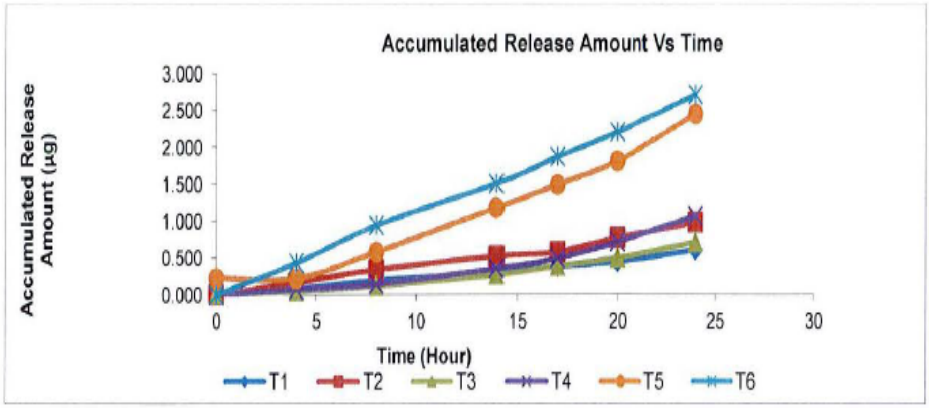
Time (hours)	G1 (control)	R1	R2	R3	R4	R5	R6	Mean
0	0.000	[redacted] (b) (4)						0.020
4	0.000							0.169
8	0.000							0.338
14	0.012							0.510
17	0.025							0.602
20	0.014							0.701
24	0.014							0.820

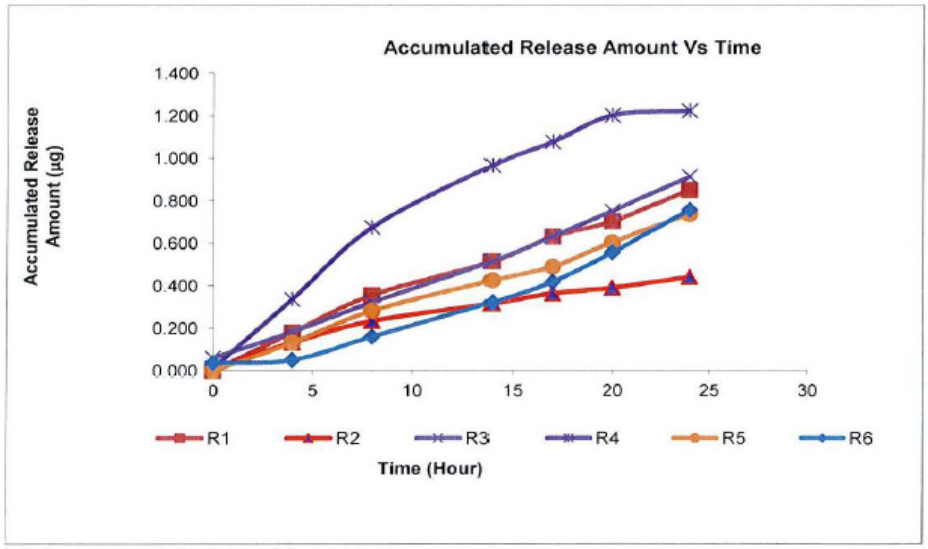
Accumulated Release Amount (µg); Test Lot# 78608 for Donor 2

Time (hours)	T1	T2	T3	T4	T5	T6	Mean

0	(b) (4)	0.040
4		0.172
8		0.389
14		0.691
17		0.869
20		1.077
24		1.422

Cumulative amount of Acyclovir versus time from test lot for donor 2





Donor 3

Summary of flux results from test lot for donor 3

Time point h	Mid-time h	Flux (µg/cm²/h) test lot							
		T1	T2	T3	T4	T5	T6	Mean	SD
0	0	[redacted] (b) (4)						0.000	[redacted] (b) (4)
4	2.0							-0.001	
8	6.0							0.002	
14	11.0							0.002	
17	15.5							0.002	
20	18.5							0.001	
24	22.0							0.003	

Summary flux results from reference lot for donor 3

Time point h	Mid-time h	Flux (µg/cm²/h) reference lot							
		R1	R2	R3	R4	R5	R6	Mean N=5	SD N=5
0	0	[redacted] (b) (4)						0.000	[redacted] (b) (4)
4	2.0							0.001	
8	6.0							0.002	
14	11.0							0.000	
17	15.5							0.003	
20	18.5							0.001	
24	22.0							-0.001	

Accumulated Release Amount (µg); RLD Lot# A4001 for Donor 3

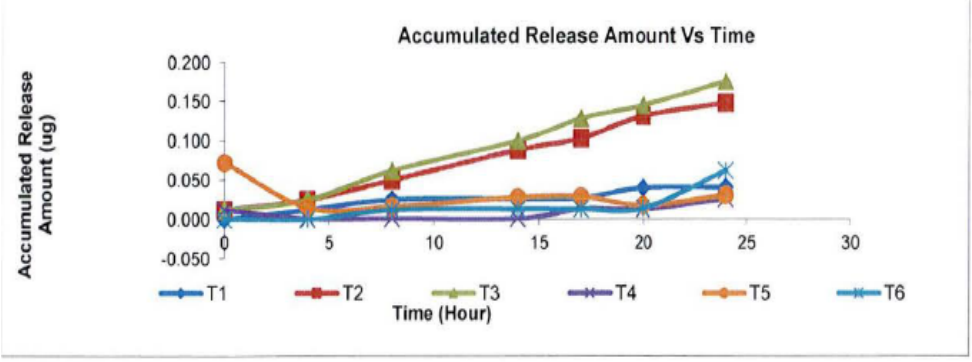
Time (hours)	G1 (control)	R1	R2	R3	R4	R5	R6	Mean (n=5)
0	0.000	[redacted] (b) (4)						0.007
4	0.012							0.015
8	0.001							0.025
14	0.001							0.024
17	0.001							0.041
20	0.001							0.048
24	0.013							0.043

Accumulated Release Amount (µg); Test Lot# 78608 for Donor 3

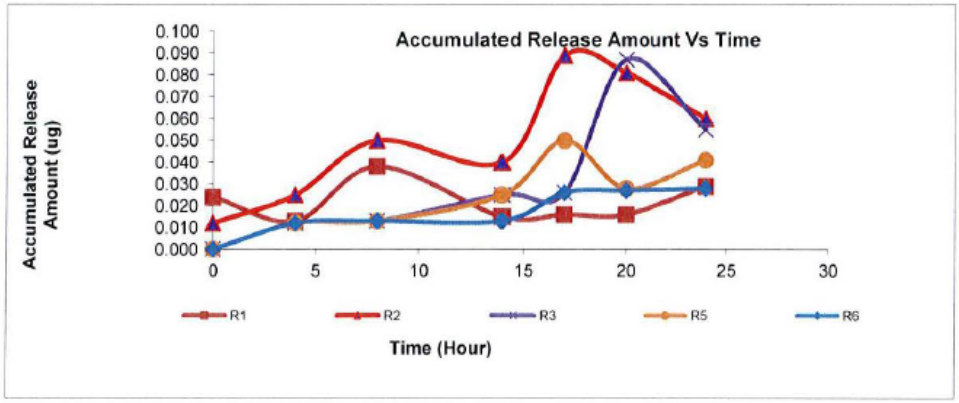
Time (hours)	T1	T2	T3	T4	T5	T6	Mean

0	(b) (4)	0.018
4		0.013
8		0.028
14		0.043
17		0.052
20		0.060
24		0.081

Cumulative amount of Acyclovir versus time from test lot for donor 3



Cumulative amount of Acyclovir versus time from reference lot for donor 3



Reviewer's comment:

For each donor, there were six replicates for both test and RLD product. The permeation profiles of each replicates showed high variability within donor for both products.

It is noted that for both test and RLD, the mean flux values for Donor 1 and 3 are comparable across all time points from 0-24 hours. However, the mean flux values for Donor 2 are higher than Donor 1 and 3. This is consistent with the lower electrical resistance values observed in Donor 2 (please see above Skin Integrity test for details).

It is noted that, in the current pivotal IVPT study, the overall amounts of acyclovir permeated into the receptor medium were very low for both Test and Reference, especially for donor 1 and 3. The firm stated that comparison of the steady flux from the products was not attempted considering very low level of acyclovir released into the receptor medium.

Reviewer did not conduct statistical analysis on the firm's IVPT pivotal flux data considering that 1) very high variability shown in the six replicates for each donor; 2) significantly different flux values between Donor 2 and Donor 1 and 3; 3) the 'irregular' flux profile trend and patterns for Donor 1, 2 and 3; 4) the study design is not acceptable, as discussed in section 3.5.1; and 5) pivotal study is not adequately powered.

- **Distribution and Mass Recovery**

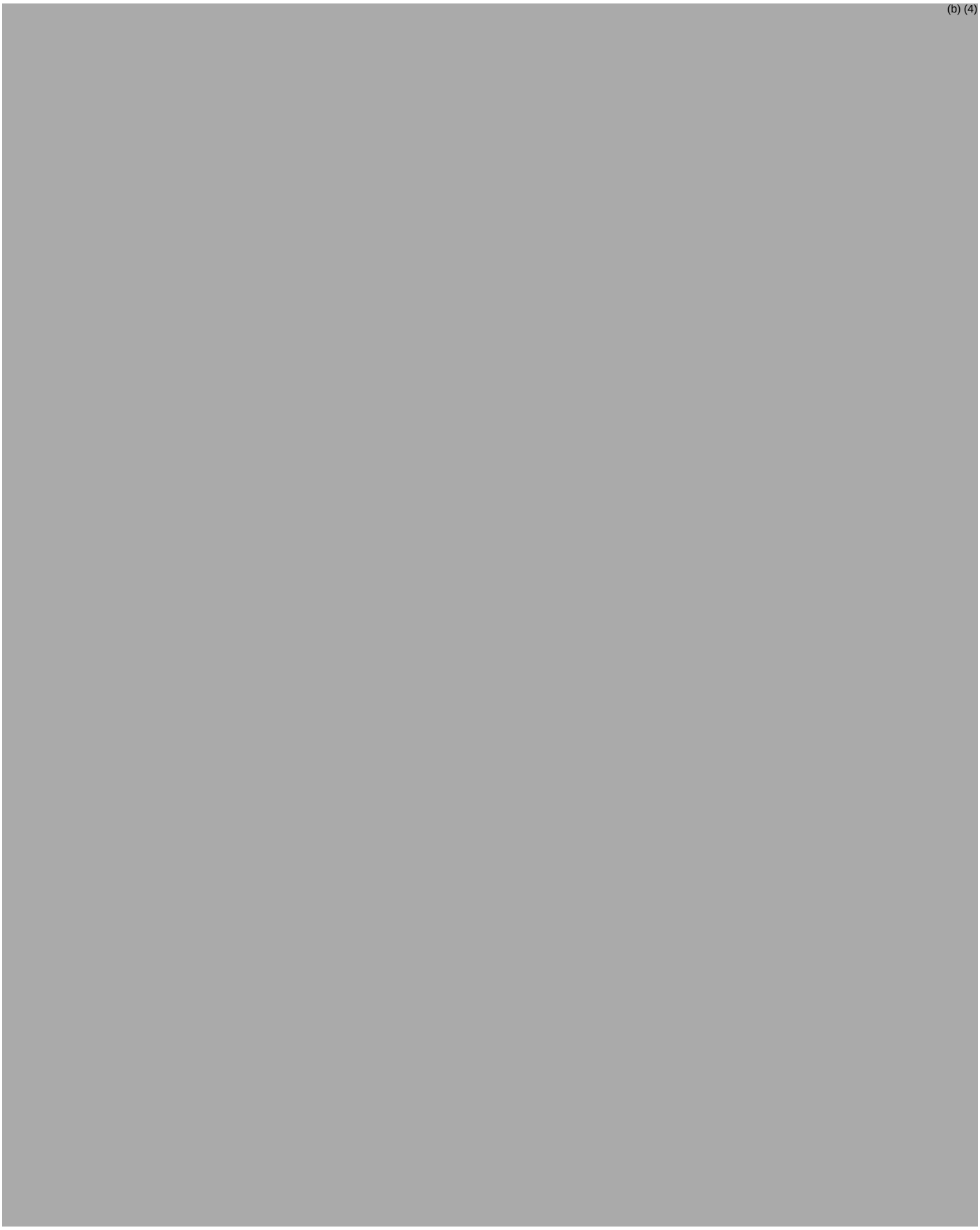
Distribution of acyclovir following a dose exposure of 24 hours to ex vivo human torso skin is presented as mass recovered per dosing area and as percent of total distribution.

(b) (4)

Table Mass balance and distribution of Acyclovir for Test

% Total Mass Balance Recovery of 3 Donors Mean for Test

(b) (4)



Reviewer's Comment on Mass Balance and Distribution:

Please note that in the revised BE guidance, the mass balance and distribution results for the IVPT study are not recommended. The primary factors for bioequivalence determination are parameters that characterize the rate and extent to which acyclovir permeates into and through the skin, and becomes available in the receptor solution.

Reviewer's overall comments for the IVPT pivotal study:

- The firm used vertical Franz cells which is common for the IVPT study. However, as discussed in Section of IVPT method development (Section 3.5.1), the firm should justify 1) why the donor chamber was kept covered during IVPT study, 2) skin surface temperature control.

- According to the firm, human torso skins (thigh region, 0.7-1.2 mm) from 3 donors (6 replicates for each donor) obtained from a tissue bank (b) (4) were used in the IVPT study. The dermatomed and cryopreserved skin was stored at -20°C before experiment. However, the following information regarding the skin samples used for the IVPT study were not provided:

    - Donor demographics (age, gender and race) for skin donors.
    - The temperature and duration of skin storage as well as the number of freeze-thaw cycles for each donor's skin.
    - Skin thickness should be measured and reported for each skin section. According to the firm, the thickness of skin is in the range of 0.7-1.2 mm.
    - The anatomical region and the harvesting/processing procedures should be consistent for all donors in the study. Skin with tattoos, stretch marks or any sign of dermatological abnormality should be excluded from the study.

- It is reasonable to randomize the assignment of skin sections from a donor to each treatment group, potentially making allowance to balance the distribution of skin thicknesses in each treatment group by a procedure pre-specified in the study protocol. It is no clear how the skin sections in each treatment group were assigned for IVPT studies.
- It is recommended that IVPT data be obtained from multiple donors because each individual has different extent of permeation and different flux profile because of the nature of the skin. The firm should properly power the study.

- One lot each of the Test (lot# 78608) and Reference (lot#A4001) products were used in the IVPT study.

- Per the revised BE guidance, the bioequivalence of the test and reference products can be examined by the maximum rate of acyclovir permeation (Jmax) and the extent of acyclovir permeation (total cumulative amount of acyclovir permeated into the receptor solution) across the study duration. For the current pivotal IVPT study, statistical analysis of the flux between Test and Reference was not performed due to 1) skin integrity test results issue (majority of skin sections from Donor 2 failed the acceptance criteria), 2) IVPT method development and validation deficiencies, 3) flux profiles issue on elimination phase, 4) pivotal study not adequately powered.

- The secondary results obtained from IVPT studies are drug distribution and mass balance accountability data. These data may be less meaningful than the dermal pharmacokinetic results because the amount of the drug in the epidermis, for example, is a snapshot at one moment in time across the entire study duration, and in a traditional study design this would be a point in time well after the Jmax.

  It is noted that the firm submitted two sets of total mass balance recovery and distribution data for test and reference products in the raw excel data sheet, one titled as "% distribution for 3 donors mean" which is shown below, and the other as "%distribution for 18 vessels" which is shown above on page 59 of this review. Firm will be requested to explain why there were two different result tables and figures for the total mass balance and distribution for pivotal IVPT studies.

Overall, the firm's IVPT study is inadequate.

3.6 OSIS Status

3.6.1 IVRT Test Site at Perrigo

OSIS conducted the inspection from May 9-11, 2016 at Perrigo Company, Parsippany, NJ auditing the IVRT study Perrigo Israel Pharmaceuticals, Yeruham, Israel (Perrigo) conducted for ANDA 208702. The inspection outcome is classified as OAI in the review of EIR for Perrigo.

- **Review of OSIS Report**
  - **OSIS Observations**

    Following inspection, a Form FDA 483 was issued with three observations as follows:

    - **Observation #1**

      Firm did not retain reserve samples of RLD lot#E3001 from the drug shipment used in the 68024 study.

      The firm's response indicated that reserve samples were not available from the shipment of lot# E3001. As a corrective action, Perrigo revised its SOP "Testing and Comparing the In Vitro Release of Drug Products following Scale-up, Post Approval Changes and bioequivalence In-Vitro Release Studies (IVRT)" to clarify the requirements on reserve samples retention. In addition, the OSIS reviewer could not confirm whether RLD lot #A4002 used in the amended IVRT testing was retained reserve samples or not.

      The authenticity of reference products RLD lot #E3001 and A4002 used in the IVRT studies conducted at Perrigo cannot be confirmed because reserve samples were not randomly selected and retained at the study site.

      Reviewer's comment:

      The Division of Bioequivalence II (DB II) concurs with OSIS that in the absence of reserve samples for RLD lots #3001 and A4002 at the study site, the authenticity of test and reference drug products used in the studies cannot be confirmed. This will be further discussed in the Reviewer's overall comment below.

    - **Observation #2**

Firm did not report all comparative in vitro release test results during the study. Specifically, the following comparative in vitro release tests were performed but not reported:

Reference Lot # F3002 vs. Test Lot # 070087 performed on 3/19/2014
Reference Lot # E3001 vs. Test Lot # 070087 performed on 6/1/2014
Reference Lot # H3003 vs. Test Lot # 078607 performed on 5/26/2015
Reference Lot # L3004 vs. Test Lot # 078607 performed on 5/27/2015
Reference Lot # F3002 vs. Test Lot # 078607 performed on 5/31/2015
Reference Lot # A4002 vs. Test Lot # 070087 performed on 7/1/2015

Reviewer's comment:

Firm submitted amendment dated 06/01/2016 containing the additional IVRT studies that firm conducted but not submitted in the original submission. Please see details in Sections 3.4.4 and 4.4 for reviews of these additional IVRT studies. Therefore, the firm's response to Observation #2 is acceptable.

- **Observation #3**

Firm did not maintain adequate drug accountability records on all test products used in the in vitro release test. Specifically, there were no records indicating the quantities and lot numbers of test drug products used for the study. The quantities of test drug products used for the study cannot be fully reconstructed from available documentation.

In response to the Observation #3, firm has revised its SOP to maintain drug accountability records for all test products from initial request until samples are discarded. OSIS reviewer finds that firm's corrective action is adequate for future studies.

Reviewer's comment:

Considering that these are in vitro BE studies of topical products, lack of drug accountability records on test products is deemed acceptable from the perspective of bioequivalence.

- OSIS Conclusion for all the inspectional observations

Following an evaluation of the inspectional findings, the OSIS reviewer recommends that the IVRT studies 68024 be partially accepted for further Agency review.

A) Experiments comparing RLD product lots to test product lots

Reference Lot	Test Lot	Testing Date	Report Reference #	Recommendation
E3001	070087	03/19/2014	68024-V2 68024-V3	**Not Acceptable**
F3002	070087	03/20/2014	68024-V3	**Acceptable**
E3001	070087	06/01/2014	68024-V3	**Not Acceptable**
H3003	078607	05/26/2015	68024-V3	**Acceptable for review as a study that did not meet acceptance criteria**
L3004	078607	05/27/2015	68024-V3	**Acceptable for review as a study that did not meet acceptance criteria**
F3002	078607	05/31/2015	68024-V3	**Acceptable for review as a study that did not meet acceptance criteria**
A4002	070087	07/01/2015	68024-V3	**Not Acceptable**
A4003	070087	07/06/2015	68024-V2 68024-V3	**Acceptable**
A4001	070087	07/07/2015	68024-V2 68024-V3	**Acceptable**

- **Reviewer's Overall Comment**

  - Reviewer concurs with the OSIS evaluation that firm's IVRT studies be partially acceptable for review due to the reserve sample issue.

  - It is noted that ANDA 205591 (Acyclovir Ointment) has a similar issue as the current one in terms of not retaining reserve samples. The Office of Bioequivalence management has decided to ask the firm to re-conduct in-vitro BE studies[15].

  - For the current application, firm has submitted multiple IVRT studies using several batches of RLDs. The IVRT studies using RLD batches E3001 and A4002 with reserve sample issues are not acceptable for review here. However, the pivotal IVRT studies using other RLD batches are acceptable for review (please see Section 3.4.4 for details). Please note that firm only needs to provide IVRT data on one batch of test product comparing to one batch of RLD product.

3.6.2 IVPT test site at (b) (4)

- The OSIS memo[12] recommends accepting the IVPT data for ANDA 208702 without an on-site inspection, as OSIS recently inspected the site (b) (4) (b) (4) and the inspectional outcome was classified as No Action Indicated (NAI).

- However, it is noted that although the inspectional outcome was classified as NAI, one objectionable finding was identified, that (b) (4) did not retain reserve samples for in vitro BE studies conducted for ANDA 205591 and 207028. Because of this observation, the authenticity of test and reference drug products used in the in-vitro BE studies for ANDA 205591 and ANDA 207028 could not be confirmed. Therefore, the OSIS recommended the in vitro BE data, specifically, GWL-AR-004-13-R00 (ANDA 205591) and DRL-AR-004-14-R00 (ANDA 207028), should not be accepted for Agency review[13].

- In BE amendment review of ANDA 205591 dated 10/14/2016[14], the firm was requested to re-conduct the IVRT studies due to the reserve sample issue.

- According to the OSIS EIR review[14], (b) (4) did not retain reserve samples for any of the studies conducted until the time of the inspection.

- The IVPT study for the current application was conducted on 10/28/2015, which was one and half month after the above mentioned inspection. Currently, reviewer could not locate information regarding retention of reserve samples in the firm's submission for the current ANDA 208702. Therefore, at this point, it is unclear whether (b) (4) retained reserve samples for the current pivotal IVPT study.

- The firm will be requested to clarify whether it retained reserve samples for the current IVPT study #PER-005-15-R00. The firm will be informed that studies without retaining reserve samples will not be acceptable for review..

(b) (4)

[14] GDRP document: ANDA-205591-ORIG-1-AMEND-10, A205591N000DB_NA07012016.pdf

4 APPENDIX

4.1 Controlled Correspondence – Q1/Q2 formulation review

Perrigo Pharmaceuticals submitted controlled correspondence (#12-0482)[15] to the Office of Generic Drugs (OGD) on 05/07/2012, requesting confirmation of Q1/Q2 compliance of its proposed formulations for Acyclovir Cream 5%. The firm proposed formulation of Acyclovir Cream, 5% in CC #12-0482 as follows:

Table 1 Proposed Formulation of Perrigo
Acyclovir Cream, 5%
Q1/Q2 matching to the RLD
Zovirax®, (acyclovir cream, 5%)

Ingredient	Concentration proposed in the Perrigo Q1/Q2 Formulation % (w/w)	Maximum Listed Limit in FDA Inactive Ingredients Database for Topical Use
Acyclovir	5.00	(b) (4)
Cetostearyl alcohol	(b) (4)	
Mineral oil		
Poloxamer 407		
Propylene glycol		
Sodium lauryl sulfate		
White petrolatum		
Water		

On 07/13/2012, Agency informed the firm that the proposed formulation is Q1/Q2 to the RLD[9].

[15] \cdsnas\OGDS6\CONTROLS\2012-docs\12-0482.pdf

4.2 Formulation Data

4.2.1 Test Formulation[16]

Ingredient	Function	Quality standard	Quantity		
			g/5g tube	% (w/w)	ANDA and commercial batch (100 Kg) Kg
ACTIVE:					
Acyclovir	Active Ingredient	USP	0.25	5*	5*
INACTIVE INGREDIENTS:					
White Petrolatum, USP	(b) (4)	USP	(b) (4)		
Cetostearyl Alcohol, NF		NF			
Mineral Oil, USP		USP			
Propylene Glycol, USP		USP			
Sodium Lauryl Sulfate, NF		NF			
Poloxamer 407, NF		NF			
Purified Water (USP, EP)		USP			
TOTAL			**5g**	**100%**	**100Kg**

(b) (4)

Reviewer's Comment:

- The test product, Acyclovir Cream 5% has the same route of administration, dosage form and strength as the RLD.

- The test product contains same active and inactive ingredients in the same amount as the RLD. Therefore, it is qualitatively (Q1) and quantitatively (Q2) the same as the RLD.

[16] DARRTS ANDA 208702 SD-1 dated 01/07/2016 Module 3.2.P.1 Description and Composition of the Drug Product
[17] DARRTS NDA#021478 FRM-ADMIN-42(Action Package) on page 91 of 197, by Smith, Lonnie D, dated 9/30/2005 http://darrts fda.gov:9602/darrts/ViewDocument?documentId=090140af8013e80d

- Thus, the formulation is **adequate.**

4.3 Physicochemical Characterization

The firm has submitted physicochemical characterization data demonstrating that their test product formulation is Q3 when compared to the RLD product formulation. Physicochemical characterization data have been reviewed by the Division of Chemistry and deemed inadequate with deficiencies (please note that the Drug Quality Review is yet to be finalized as of 03-02-2017)[18].

(b) (4)

4.4 Attachments

4.4.1 Additional IVRT Studies Firm submitted

Following OSIS inspection, firm submitted 6 additional IVRT studies comparing different RLD products to test product as follows:

[18] GDRP document: ANDA-208702-ORIG-1»Drug Product Quality Review, A208702 DS DP LBL R01.docx

Study Date	Reference Batch /Expiry Date	Test Batch / Manufacturing Date
March 19, 2014 *	RLD E3001 / May, 2016	070087/ December, 2013
March 20, 2014	RLD F3002/ June, 2016	070087/ December, 2013
June 1, 2014	RLD E3001/ May, 2016	070087/ December, 2013
May 26, 2015	RLD H3003/ August, 2016	078607/ October, 2014
May 27, 2015	RLD L3004/ October, 2016	078607/ October, 2014
May 31, 2015	RLD F3002/ June, 2016	078607/ October, 2014
July 1, 2015	RLD A4002/ January, 2017	070087/ December, 2013
July 6, 2015 *	RLD A4003/ January, 2017	070087/ December, 2013
July 7, 2015 *	RLD A4001/ January, 2017	070087/ December, 2013

*Studies submitted in original ANDA #208702 for Acyclovir Cream, 5%.

Additional IVRT study #1 (RLD batch #F3002 vs. Test #070087)

(b) (4)

[redacted]

Table 5: Slopes and Ratio of Slopes of Comparative *In-Vitro* Release Test of Acyclovir from Acyclovir Cream, 5%, Batch #070087 and Zovirax Acyclovir Cream, 5%, Batch #F3002

		Reference F3002					
	Test	1	2	3	4	5	6
		(b) (4)					
1	[redacted]						
2							
3							
4							
5							
6							

***Note:** The SST of the test on March 19, 14 didn't meet the acceptance criteria, therefore the test was repeated on March 20, 14.

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

- For the failed IVRT studies, firm stated that investigations revealed that the failure could be attributed to phase separation and nonhomogeneous appearance of these batches.

- Firm provided pictures for comparison of RLD batches E3001 (b) (4) vs. H3003 (b) (4)) as follows:

- Firm did not specify if all IVRT studies were conducted under the same conditions or not. It is under the assumption that all IVRT studies were conducted under the same condition.

- Based on all facts stated above, reviewer agrees that the firm's reasoning is acceptable on the failed IVRT studies.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 208702

APPLICANT: Perrigo UK FINCO Limited Partnership

DRUG PRODUCT: Acyclovir Cream, 5%

The Division of Bioequivalence II (DBII) has completed its review and has identified the following deficiencies:

In December 2016, the Agency posted revised draft guidance on this drug product. This revised draft guidance provides updated product-specific recommendations for establishing bioequivalence (BE) to Zovirax® (acyclovir) Cream (NDA 021478). Please refer, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428195.pdf, for details on *in-vitro* options to compare your test product, Acyclovir Cream, 5 % w/w, to the corresponding reference listed drug (RLD) product, Zovirax® (acyclovir) Cream, 5 % w/w.

In Vitro Release Test (IVRT) Study

Method Development and Validation:

1. Please submit detailed method development procedures and report for IVRT method including all supportive data as it relates to the method development of the IVRT per the current guidance for this drug product. The report should include but is not limited to:

    a. Explanation for the choice of amount of sample used
    b. Explanation for the choice of receptor medium. Please submit supporting data, such as report #63767 as you mentioned in your IVRT method development report #66310-v1
    c. Explanation for the choice of sampling times, stirring rate
    d. Evaluation of membrane inertness
    e. Your IVRT method development report #66310 lacks details and supporting data. Please submit detailed method development report.

2. Please provide IVRT method validation data for the following parameters per the revised guidance for this drug product:

    a. IVRT Linearity and range
    b. IVRT Recovery, mass balance and dose depletion
    c. IVRT method discrimination sensitivity, specificity and selectivity
    d. IVRT Method robustness

3. You submitted method precision and inter-analyst intermediate precision data, but did not use the appropriate approach. Please evaluate the method precision and reproducibility following the current BE guidance for this drug product.

Pre-Study Analytical Method Validation

4. Your pre-study bioanalytical (HPLC) method validation report did not include limit of detection (LOD) and robustness for your analytical method. Please submit this information.

5. The acyclovir stability should be evaluated under the highest relevant temperature in the receptor solution for the duration of the IVRT study. Please submit the stability assessment data following the revised BE guidance.

Pivotal IVRT Study

6. You conducted sample analysis based on single point external stand (b) (4). It is noted that the acyclovir concentrations in the receiving media ranged from μg/mL which is not a narrow range. Please use validated multiple point calibration standards and quality control samples for quantitation of acyclovir in the IVRT samples.

7. You conducted the in vitro release tests using the Franz Diffusion Cell apparatus. However you did not provide details on how the test was conducted and what parameters were used. For example, it is not clear if (1) the membrane was pre-soaked and for how long, (2) the receptor medium was degassed, (3) the stirrer was stopped during sampling. Please submit a detailed systematic procedure and report of the setup and operation of the Vertical (Franz) Diffusion Cell and about the parameters 1, 2 and 3 requested above.

8. Please submit raw data for the IVRT testing in electronic SAS Transport format.

In Vitro Permeation Test (IVPT) Study

Method Development and Validation

9. You have submitted an IVPT method development report. However, your method development is not acceptably comprehensive to cover all the key aspects of the method. Please provide the following additional IVPT method development information as suggested in the current guidance:

   a. Explanation of study apparatus related parameters, *e.g.* (1) the choice of receptor chamber stirring rate, (2) rationale for having the epidermal chamber covered during IVPT study (please note that the current guidance recommends un-occluded condition); and (3) the skin surface temperature measurement/control.

   b. Please provide details on the initial IVPT testing procedures and results, and explain (1) what are the blank and placebo samples used in the initial IVPT testing, whether skin samples were used in the blank and placebo samples, (2) for the linearity results, on page

7 of the submitted Method development report #PER-AR-006-15-R00, why the SPE method gave significantly higher response for STD1/2 to STD10 than the neat curve and PPT method.

c. Please justify the acceptance criteria of electrical resistance value of (b) (4) the reading of the diffusion medium, for the skin integrity test.

d. Please justify the choice of receptor medium and provide solubility data of acyclovir in the selected receptor medium. Please note that an anti-microbial agent may be needed in the receptor medium.

e. Per the current guidance, the sampling time points and duration should be justified based on a pilot study. The duration of an IVPT study should be sufficient to characterize the majority of the dermal pharmacokinetic profile, or at least a sufficient amount of the flux profile to identify the maximum flux and a decline in the flux thereafter across subsequent time points.

f. The dose utilized in the IVPT study should be justified. Different dose amounts may be compared to evaluate the IVPT method.

g. Your pilot IVPT study only included skin samples from one donor. The current guidance recommends that a pilot IVPT study should have a minimum of 4 replicate skin sections per donor from multiple donors to support the development of appropriate conditions for the pivotal IVPT study.

10. It is noted that significant interferences at the retention time of acyclovir were observed in the blank samples without drug product in your IVPT specificity study. It is mentioned in your report that the interference probably came from endogenous substances in the skin. Per the current guidance, skin from donors with significant background levels of acyclovir or other compounds that may interfere with the quantitation of acyclovir in receptor solution samples should be excluded from the study. Please explain your inclusion and exclusion criteria for choice of skin samples.

11. Please provide IVPT method validation data for the following parameters per the revised guidance for this drug product:

    a. IVPT precision and reproducibility
    b. IVPT Recovery, mass balance and dose depletion
    c. IVPT discrimination, sensitivity and selectivity
    d. IVPT Method robustness

12. Please validate the IVPT method for the study apparatus, methodologies and study conditions per the current BE guidance for this drug product.

<u>Pre-Study Analytical Method Validation</u>

13. Your analytical method validation report (PER-AR-004-15-R00) was mostly conducted using neat standard solutions only, which is not acceptable relating to the matrices relevant to the IVPT study. The sample analysis procedures should be validated in a manner comparable with the current FDA Guidance for Industry on Bioanalytical Method Validation and/or the ICH Harmonized Tripartite Guideline on Validation of Analytical Procedures Q2 (R1). Parameters to be validated include, but are not necessarily limited to, the following:

    a. Specificity, Selectivity, and Identification
    b. Linearity and Range
    c. Accuracy and Precision
    d. Sensitivity (Detection Limit and Quantitation Limit)
    e. Robustness
    f. Stability
    g. Recovery

Pivotal IVPT study

14. Study protocol should include inclusion and exclusion criteria for skin donor selection.

15. It is noted that multiple skin sections failed to meet your skin integrity test criteria [Donor 1 (Vessel #5 for both T and R), and Donor 2 (Vessel #1R, 2T; Vessels #3, 4, 5 and 6 for both T and R)]. According to your study protocol, only skin sections with electrical resistance value of ≥3times the reading of the diffusion medium can be used for the IVPT test. Please explain why the skin sections that failed the skin integrity test criteria were still used for the IVPT test. It is also noted that the flux values for Donor 2 are higher than Donor 1 and 3.

.

16. The following information should be provided for the skin samples, (1) skin thickness for each skin section; (2) skin donor demographics (age, gender, and race); (3) skin storage information; (4) if skin sections from each donor were randomized to each treatment group.

17. Please ensure that your pivotal IVPT study is adequately powered.

18. You submitted two sets of total mass balance recovery and distribution data for test and reference products in the raw excel data sheet, one titled as "% distribution for 3 donors mean", and the other as "%distribution for 18 vessels". It is noted that the results table and graphs in these two Excel data sheets were not consistent. Please explain this discrepancy.

19. We could not locate information on randomly selected and retained the reserve samples for both test and reference products used in your pivotal IVPT study #PER-005-15-R00. Based on 21 CFR 320.38 and 320.63, samples should be retained and stored at study sites, or at independent third parties. Please clarify if you retained reserve samples of test and reference products for the IVPT studies. Please note that studies without retaining reserve samples will not be acceptable.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R. Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 COMPLETED ASSIGNMENT FOR 208702 ID: 29948

Reviewer: Li, Li **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Acyclovir Cream 5%

Items:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Score***	***Subtotal***
29948	1/7/2016	BIO	ANDA Original [1]	1	1
29948	1/7/2016	BIO	OSIS Inspection Report Review [1]	1	1
29948	1/7/2016	Parallel	In Vitro Studies (Other: IVIVC, IVPT, IVRT, GSD, QCRT) (Per study for all strengths) [1]	2	2
29948	1/7/2016	Parallel	OSIS Inspection Report: Review of Parent (Per application) [1]	1	1
29948	1/7/2016	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation [0.25]	0.25	0.25
				Total:	5.25

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

STATISTICAL REVIEW(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA Number	208702
Drug Name	Acyclovir Cream, 5%
Applicant	Perrigo UK FINCO Limited Partnership
Reference Listed Drug	ZOVIRAX® (Acyclovir) Cream, 5%
Indication	Treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.
Date(s)	FDA Received Date: August 24, 2017 Review Assignment Date: April 18, 2018 Statistical Review Goal Date: September 27, 2018
Biometrics Division **Statistical Primary Reviewer** **Statistical Secondary Reviewer**	DBVIII Somesh Chattopadhyay, Ph.D. Yu-te Wu, Ph.D., Team Leader
Clinical Division **Clinical Primary Reviewer** **Clinical Secondary Reviewer**	OGD/OB/DCR Raquel Tapia, M.D. Carol Kim, Pharm.D., Clinical Team Leader
Deficiency Classification	☐Major ☐Minor ☐Not Applicable
Major Deficiency Theme	☐New Studies Needed ☐Inconsistent Information ☐Unresolved Statistical Issues ☐Other
Justification of Major Deficiency Designation	
Keywords	active control/clin. equivalence, endpoint analysis/LOCF, modified intent-to-treat, per protocol

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant has submitted results from one multicenter, randomized, double-blind, vehicle-controlled, parallel group study to compare the test product Acyclovir cream, 5% (Perrigo) and the reference product Zovirax (acyclovir) cream 5% (Valeant Pharmaceuticals) for the treatment of recurrent herpes labialis. The test and reference products showed equivalence with respect to time to complete healing in the per-protocol (PP) population. However, both test and reference products failed to show statistically significant superiority over the vehicle cream with respect to time to complete healing in the FDA's modified intent-to-treat (mITT) population. The study lacked assay sensitivity. Therefore, bioequivalence between the test and reference products cannot be established.

1.2 Brief Overview of Clinical Studies

The review is based on the only clinical study PRG-NY-14-008 submitted in this application. Study PRG-NY-14-008 was a multicenter, randomized, double-blind, vehicle-controlled, parallel group bioequivalence study of acyclovir cream, 5% and Zovirax cream, 5% in subjects with recurrent herpes simplex labialis. Subjects were randomized in a 1:1:1 ratio to three treatment arms: Acyclovir cream, 5% (Perrigo), Zovirax (acyclovir) cream 5% (Valeant Pharmaceuticals) and Vehicle (control) of acyclovir cream (Perrigo). A total of 4076 subjects were randomized, 1357 to the test product, 1361 to the reference product and 1358 to the vehicle. The first subject was enrolled on October 6, 2014 and the last subject completed the study on April 27, 2016. Subjects were enrolled at 96 centers in the USA. Primary evaluation of bioequivalence was determined using the per-protocol population by comparing the time to complete healing in each treatment group.

1.3 Statistical Findings and Issues

This application is based on a clinical endpoint bioequivalence study PRG-NY-14-008. The test and reference arms showed equivalence with respect to time to complete healing in the per-protocol population [90% confidence interval: (0.92, 1.05)]. Neither the test nor the reference arm showed statistically significant superiority over vehicle arm with respect to time to complete healing [two-sided p-values 0.8646 and 0.9864, respectively] in the FDA's mITT population. The equivalence and superiority analyses of time to complete healing are shown in Table 8 and Table 9, respectively. The test and reference products also showed equivalence between them in the FDA's mITT population with respect to time to complete healing.

The following statistical issues were identified.

1. The test and reference products showed equivalence. However, both test and reference products failed to show statistically significant superiority over vehicle. Therefore, the study does not have assay sensitivity and cannot be used to establish bioequivalence.

2. The applicant's definition of the primary endpoint matches with the recommended primary endpoint, the duration of episode (DOE), in FDA's Draft Guidance on Acyclovir for subjects who experience a vesicular lesion. For subjects whose primary lesion was not vesicular, the draft guidance recommends DOE to be defined as the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last. However, the applicant did not provide any definition of time to complete healing in the case of non-vesicular primary lesion. The applicant censored the subjects with non-vesicular lesions at time 0 (time of first dosing).

3. The applicant used the same definition for the safety and ITT populations. The definition is consistent with the generally used definition for the ITT population but not the safety population. The subjects should have taken at least one dose of study medication to be included in the safety population and should be classified as treated, not as randomized.

4. FDA's current definition of the mITT population is different from that of the applicant. FDA's mITT population includes all subjects who were randomized and received at least one dose of study treatment. In this case, this definition is same as the definition of the FDA's safety population.

2 INRODUCTION

2.1 Overview

2.1.1 Background

The herpes simplex virus (HSV) presents in 2 forms: HSV-1 and HSV-2. HSV-1 (herpes labialis or orolabial herpes) is the most common cause of cold sores and usually affects the areas on or around the mouth. It is estimated that roughly 50 million people in the United States show symptomatic recurrences of the virus every year. The virus is highly contagious and can be spread easily through direct contact, even if the cold sore is not present. After initial infection, the virus lies in the trigeminal ganglion, where it can be "reactivated" from a variety of causes such as stress and weather changes. Many subjects experience a period before the lesion appears known as the prodrome phase (pain/burning/stinging/itching/tingling, etc.) in which treatment should begin. In roughly one-third of infected individuals, the virus reactivates multiple times a year to form the cold sore via nerve endings.

A classic lesion is defined as an ulcerative lesion that undergoes stages of vesicle, ulcer/soft crust and/or hard crust formation. Lesion stages may be assessed as follows:

- Prodrome: symptoms including itching, pain, tingling, etc., but no physical evidence of disease by inspection or by palpation in the application area
- Macule: erythema in the application area
- Papule: any elevation of skin without fluid in the application area
- Vesicle: blister, fluid filled or collapsed, in the application area
- Crusted: soft or hard crust in the application area
- Healed: loss of crust and re-epithelialization with or without erythema

A classical episode involves a localized recurrence which progresses from the vesicular (or later) stage through complete healing. An aborted episode is defined as a typical, recurrence-associated localized, site-specific prodrome and/or redness and/or papule, which completely resolves without ever progressing to the vesicular stage.

The cold sore typically heals within 2 weeks; however, the virus remains dormant for the duration of the infected individuals' life. Zovirax® (acyclovir) cream 5% is indicated for the topical treatment of herpes labialis. The applicant is seeking approval of a generic formulation of acyclovir cream 5%.

2.1.2 Regulatory History

The reference listed drug Zovirax® (Acyclovir Cream, 5%) was approved by FDA under NDA 021478 on December 30, 2002 for the treatment of herpes labialis.

2.1.3 Specific Studies Reviewed

In the current submission, the applicant submitted results from one clinical endpoint bioequivalence study (PRG-NY-14-008). This review is based on this single study.

Study PRG-NY-14-008 was a multicenter, randomized, double-blind, vehicle-controlled, parallel group bioequivalence study of acyclovir cream, 5% and Zovirax cream, 5% in subjects with recurrent herpes simplex labialis. The study randomized 4076 subjects to either Acyclovir cream, 5% (Perrigo) (test) or Zovirax (acyclovir) cream 5% (reference) or Vehicle cream (Perrigo) in a 1:1:1 ratio. The assigned treatment was to be applied five times a day for 4 days, as soon as they experienced the onset of signs or symptoms (prodrome) of herpes labialis, within 1 hour and before the clinical sign of a cold sore (blister). The study consisted of a screening Visit, Visit 2 (Day 1) as soon as possible and within 24 hours upon first application of study medication, Visit 3 (Day 2), Visit 4 (Day 3), Visit 5 (Day 4), Visit 6 (Day 5), Visit 7 (Day 6), Visit 8 (Day 7) Visit 9 (Day 8), Visit 10 (Day 10), Visit 11 (Day 12), Visit 12 (Day 14) and Visit 13 (Day 21). Subjects were enrolled at 96 centers in the USA.

2.2 Data Sources

Data used for this review are from the electronic submissions dated 5 April 2018, 19 July 2018, 24 July 2018, and 23 August 2018. The paths for the data and data definition files are \\Cdsesub1\Evsprod\ANDA208702\0006\m5\datasets\prg-ny-14-008\analysis\adam\datasets, \\Cdsesub1\Evsprod\ANDA208702\0006\m5\datasets\prg-ny-14-008\tabulation\sdtm, \\Cdsesub1\Evsprod\ANDA208702\0007\m5\datasets\prg-ny-14-008\analysis\adam\datasets, and \\Cdsesub1\Evsprod\ANDA208702\0008\m5\datasets\prg-ny-14-008\analysis\adam\datasets.

The clinical study report, protocol and statistical analysis plan are located at \\Cdsesub1\Evsprod\ANDA208702\0006\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\prg-ny-14-008, \\Cdsesub1\Evsprod\ANDA208702\0007\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\prg-ny-14-008, And \\Cdsesub1\Evsprod\ANDA208702\0009\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\prg-ny-14-008.

3 STATISTICAL EVALUATION

3.1 Study PRG-NY-14-008

3.1.1 Study Objective

The objective of this study was to compare the safety and efficacy profile of Perrigo's acyclovir cream 5% (test product) to Valeant's Zovirax cream 5% (reference product) and to demonstrate the bioequivalence of the test product to the reference product as well as superior efficacy of the two active formulations over that of the vehicle in the treatment of herpes labialis in adults and adolescents 12 years of age and older.

3.1.2 Study Design

This was a multicenter, randomized, double-blind, vehicle-controlled, parallel group bioequivalence study of acyclovir cream, 5% and Zovirax cream, 5% in subjects with recurrent herpes simplex labialis. The subjects were to be immunocompetent (defined as not having underlying disease and/or the administration of immunosuppressant medication) male or nonpregnant females, 12 years of age and older, with non–life-threatening recurrent herpes simplex labialis. The subjects had to have at least three recurrences of herpes simplex labialis per year for the past 2 years. At least half of recurrences were to be preceded by recognizable prodromal symptoms and at least half of prodromes followed by classical lesions.

In total, 4076 subjects were enrolled and randomized at 96 sites and 2539 subjects were dosed.

Subjects who satisfied study entrance criteria were randomized to one of the following three treatment groups in 1:1:1 allocation ratio:

- Acyclovir cream, 5% (Perrigo UK Finco Limited Partnership)
- Zovirax (acyclovir) cream 5% (Valeant Pharmaceuticals)
- Vehicle (control) of acyclovir cream (Perrigo Israel Pharmaceuticals)

Subjects were instructed to apply the study medication five times a day for 4 days, as soon as they experienced the onset of signs or symptoms (prodrome) of herpes labialis (that the subject may have noticed in the past recurrences) within 1 hour and before the clinical sign of a cold sore (blister). At the screening visit (Visit 1), subjects were instructed not to apply the study medication if it could not be applied within 1 hour of prodrome onset and to instead wait for the next recurrence. However, there was a treatment initiation window of +30 minutes (not disclosed to study subjects) that the study site could allow. Subjects were instructed to call the clinic to schedule an appointment for Day 1 (Visit 2) to occur as soon as possible and within 24 hours upon first application of study medication. At this visit, the investigator evaluated the subject and identified the target area in the source document. Subjects used a diary to record each time and date of study medication application in addition to recording any adverse events (AEs) experienced or medication used.
As soon as the subject saw for the first time that the crust had completely fallen off spontaneously and new skin was seen beneath, he or she was to note the date and time of

complete lesion healing in the diary. The subject would then go to the clinic for the end of study visit as soon as possible and within 24 hours from the time of complete lesion healing to confirm healing by the investigator.

If the subject's lesion healed prior to Day 5 (Visit 6), the subject was instructed to continue to apply the study medication as proposed for 4 days, and return for all study visits up to Day 5 (Visit 6), which was to serve as the end of study visit. If the lesion had healed after Day 5 (Visit 6), but before Day 21 (Visit 13), the subject returned for the end of study visit as directed by protocol, upon healing, and did not have to continue coming to the clinic for the remaining study visits. Subjects with an aborted episode were instructed to apply study medication as proposed for 4 days, five times daily, and return for all study visits up to Day 5 (Visit 6), which would serve as their end of study visit. If healing occurred in-between scheduled study days, the subject was instructed to return to the clinic as soon as possible and not wait until the next scheduled visit. If a subject arrived at the clinic on an unscheduled visit, the subject underwent the same procedures as a scheduled follow-up day. If the subject had not healed by this unscheduled visit, the subject was instructed to return to the clinic for the subsequent previously planned follow-up visits.

The Principal Investigator delegated the task of lesion healing assessments and application site reaction assessments to qualified and experienced staff who had received training to conduct this assessment. To the greatest extent possible, the same investigator who conducted Day 1 (Visit 2) assessments for a subject was expected to perform those assessments for that subject for all subsequent visits.

Concomitant medications and any medications taken in the 30 days prior to signing informed consent/assent were recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications recorded included prescription and over-the-counter medications, as well as dietary supplements.

3.1.3 Treatment Compliance

Subjects were considered compliant if they applied at least 75% and not more than 125% of doses (15 to 25 applications), did not miss more than five consecutive applications of study medication and completed the evaluation within the designated visit window. Study staff reviewed the diary at each visit to verify compliance with protocol and use of medication. Study staff also verified use of study medication by visual inspection of the study medication tube.

3.1.4 Efficacy Endpoints

<u>Primary Endpoint:</u>

The primary efficacy endpoint in this study was the time from the first dosing to complete healing of lesions (defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on both clinical observation and review of the subject diary).

A lesion was considered healed when for the first time the crust completely fell off spontaneously and new skin could be seen beneath. Retracting crust with normal skin seen at the edges was not considered healed until the complete crust fell off spontaneously.

Subjects reported their healing of the lesion in the diary. The investigator evaluated the subject and reviewed the diary to confirm healing. If the subject did not report healing but the investigator did upon evaluation, the investigator recorded the time of healing as the time of evaluation. The subject-reported healing time was used in the analysis whenever possible.

Censoring was performed as follows:

- When complete healing did not occur/was neither reported by the subject nor the investigator by the end of study visit (Day 21), the subject was censored at 21 days. Per study design, this time corresponds to the longest time the subjects can report that healing did occur.
- The subjects who experienced an "aborted lesion" (`i.e., no lesion outbreak) were assigned a value of zero (0) for time-to-complete healing of lesions.

Exploratory and Other Efficacy Endpoints:

Other efficacy endpoints include the elapsed time, in hours, between the subject-reported lesion healing date/time and the investigator-assessed lesion healing date/time.

Lesion stages were collected via subject diaries. The protocol stated that lesion stages may have included the following categories: stage 0 (no signs), stage 1 (early signs – prodrome), stage 2 (redness), stage 3 (small blister), stage 4 (ulcer), stage 5 (crust), and stage 6 (healed lesion). Stage 0 (no signs) was not collected. The collection of lesion stage was included in the updated version of the diary, so these data are not available for all study subjects.

Reviewer's Comment:

The applicant's definition of the primary endpoint matches with the recommended primary endpoint, the duration of episode (DOE), in FDA's Draft Guidance on Acyclovir cream for subjects who experience a vesicular lesion. For subjects whose primary lesion was not vesicular, the draft guidance recommends DOE to be defined as the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last. However, the applicant did not provide any definition of time to complete healing in the case of non-vesicular primary lesion. The applicant censored the subjects with non-vesicular lesions at time 0 (time of first dosing).

3.1.5 Sample size Considerations

Sample size was based on the primary analysis of time-to-complete healing in days of the herpes labialis lesions. A difference of 0.44 days was estimated to be the efficacy margin between active

treatment and vehicle (control) treatment, with the mean time-to-complete lesion healing for vehicle being 5 days. The common SD was 2.5 days. This was based on published data examining the healing times of recurrent herpes labialis (RHL) lesions with the use of acyclovir cream 5%. A sample size of 2052 subjects in the mITT population would provide over 90% power to show a significant difference between each active treatment versus vehicle. It was anticipated that approximately 85% of mITT subjects would qualify for the PP analysis, resulting in 1745 PP subjects (with 581 subjects on each arm). This sample size provides an overall 0.82 probability of showing bioequivalence for the test and reference formulations (i.e., 90% CI on the test-to-reference ratio in the PP population would be contained between 0.80 and 1.25, primary analysis) and also showing that each active treatment was statistically superior (t-test, 2-sided, $p<0.05$) to the vehicle control in the mITT population.

The actual number of subjects enrolled in the study was based on blinded review of subject status to determine that the number of subjects expected to meet the PP criteria was sufficient. Subjects who were discontinued/withdrawn after entering the randomized treatment phase were not replaced.

3.1.6 Statistical Methods

3.1.6.1 Analysis Population

Applicant's Analysis Populations

Intent-to-Treat (ITT)/Safety Population:

The ITT/safety population included all randomized subjects who were dispensed study medication regardless of if the medication was used or not by the subject. Subjects were summarized by randomized (assigned) treatment.

Exposed to Study Drug Population:

The Exposed to Study Drug population included the subjects who were dispensed and applied study medication. Subjects were summarized by randomized (assigned) treatment.

Modified Intent-to-Treat (mITT) Population:

The mITT population included the subjects who met the following criteria:

- Met Visit 2 inclusion/exclusion criteria,
- Randomized, dispensed, and used at least one dose of the study medication, and
- Returned for at least one post-screening efficacy assessment.

Subjects were summarized by randomized (assigned) treatment.

Per-Protocol (PP) Population:

The PP population included the subjects who met the following criteria:

- Met Visit 2 inclusion/exclusion criteria,
- Randomized, dispensed, and met the protocol criteria for treatment compliance, i.e., received at least 75% and not more than 125% of intended doses and did not miss more than five consecutive doses,
- Had no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy
    - Had Visit 2 investigator assessment within +2 days of first treatment;
    - Did not take any prohibited medications;
    - Had subject-reported healing and had investigator-healing assessment within +2 days of subject-reported healing time.

Subjects who did not have subject-reported healing, but met the other criteria for PP, could have been included in the PP population per the following:

- Subjects who discontinued early (or completed the study) after completing at least 3 days of treatment, did not heal, and were declared treatment failures were included in the PP population provided that there were no other protocol violations identified prior to their discontinuation. Subjects who discontinued early (or completed the study) but were not treatment failures were excluded from the PP population.
- Subjects whose primary lesions were not vesicular in nature (aborted lesions), but initiated study treatment, completed the study, and met all the above criteria were included in the PP population.
- Subjects who did not experience a prodrome, but initiated study treatment, completed the study, and met all the above criteria were included in the PP population.

Subjects were summarized by actual treatment dispensed.

FDA's Analysis Populations

Safety Population:

FDA's safety population includes all subjects who received at least one dose of study medication.

Modified Intent-to-Treat (mITT) Population:

FDA's current definition of the mITT population is different from the applicant's definition of the mITT population. FDA's mITT population includes all subjects who were randomized and received at least one dose of study treatment.

Per-Protocol (PP) Population:

FDA's definition of the PP population is same as the applicant's definition. In addition, a subgroup of the PP population excluding the subjects with aborted lesion was considered for analysis.

Reviewer's Comment:

The applicant used the same definition for the safety and ITT populations. The definition is consistent with the generally used definition for the ITT population but not the safety population. The subjects should have taken at least one dose of study medication to be included in the safety population and should be classified as treated, not as randomized.

3.1.6.2 Applicant's Statistical Analysis Methods

Test for bioequivalence of test and reference treatments

The primary efficacy analysis was to demonstrate that Perrigo's acyclovir cream 5% (test) was bioequivalent to Zovirax cream 5% (reference).

The hypothesis to test bioequivalence of test formulation to reference formulation was:
H_0 (null hypothesis): $\mu_T/\mu_R \leq 0.80$ or $\mu_T/\mu_R \geq 1.25$
versus
H_1 (alternative hypothesis): $0.80 < \mu_T/\mu_R < 1.25$
Where, μ_T is the mean time-to-complete healing of the lesion in the test and μ_R is the mean time-to-complete healing of the lesion in the reference.

For test formulation to be considered bioequivalent to the reference formulation, the 90% confidence interval (CI) for the ratio of the means (test/reference [T/R] ratio) had to fall within the interval of 0.80 to 1.25.

The mean time-to-complete healing of test and reference product was analyzed using analysis of variance (ANOVA) with treatment and center as fixed effects in the model. The 90% CI for the ratio (T/R) of mean time-to-complete healing was obtained by Fieller's method. This analysis was performed using both the PP and mITT populations, where the PP population served as definitive analysis population and the mITT population was considered a supportive analysis population.

Test for superiority of each active treatment over vehicle treatment

The test for superiority was performed to show each of the active formulations (test and reference) was superior in efficacy over vehicle.

Two separate superiority tests were conducted, test vs. vehicle and reference vs. vehicle. The mITT population served as the definitive analysis and analysis based on the PP population was considered as the supportive one for the superiority analysis. The time-to-complete healing of both the active products and vehicle were analyzed using ANOVA evaluations with treatment and center as fixed effects in the model.

3.1.6.3 FDA's Statistical Methods

The reviewer's analysis methods for the primary analysis of bioequivalence between the test and reference products and the superiority of the test and reference products over the vehicle are same as the applicant's methods. In addition, the reviewer performed survival analyses of time-to-complete healing as sensitivity analyses.

The reviewer also performed subgroup analyses in the subjects excluding those who had aborted lesions.

3.1.7 Subject Disposition and Analysis Populations

This study randomized 4076 subjects, 1357 to the test product, 1361 to the reference product and 1358 to vehicle. Among them, 2416 subjects (793 in the test arm, 810 in the reference arm and 813 in the vehicle arm) completed the study. Subject disposition including the reasons for study discontinuation by treatment is presented in Table 1.

Table 1: Subject Disposition by Treatment Arm

	Test (N=1357)		**Reference (N=1361)**		**Vehicle (N=1358)**		**All (N=4076)**	
Completed	793	(58.44%)	810	(59.52%)	813	(59.87%)	2416	(59.27%)
Not completed	564	(41.56%)	551	(40.48%)	545	(40.13%)	1660	(40.73%)
Reason for discontinuation								
Withdrawal by subject	62	(4.57%)	62	(4.56%)	59	(4.34%)	183	(4.49%)
Subject did not experience recurrence	221	(16.29%)	227	(16.68%)	221	(16.27%)	669	(16.41%)
Subject did not meet or no longer met the entry criteria	2	(0.15%)	1	(0.07%)	2	(0.15%)	5	(0.12%)
Adverse event	6	(0.44%)	3	(0.22%)	0	(0%)	9	(0.22%)
Lost to follow-up	149	(10.82%)	153	(11.24%)	147	(10.82%)	449	(11.02%)
Aborted lesion	1	(0.07%)	3	(0.22%)	1	(0.07%)	5	(0.12%)
Pregnancy	3	(0.22%)	1	(0.07%)	3	(0.22%)	7	(0.17%)
Other	120	(8.84%)	101	(7.42%)	112	(8.25%)	333	(8.17%)

Source: Applicant's datasets and reviewer's analysis

Out of 4076 subjects, 1537 subjects were not dosed. These subjects were excluded from the safety population by FDA. The applicant did not exclude any subjects from the safety population. FDA excluded the subjects those 1537 subjects who were not dosed from the mITT population. The applicant excluded those and another 74 subjects from the mITT population. FDA's determination of PP populations matches with that of the applicant. Determination of analysis populations by the applicant and FDA is presented in Table 2.

Table 2: Applicant's and FDA's Determination of Analysis Populations

	Applicant's Determination				FDA's Determination			
	Test	**Reference**	**Vehicle**	**All**	**Test**	**Reference**	**Vehicle**	**All**
Enrolled (randomized)	1357	1361	1358	4076	1357	1361	1358	4076
Safety Population	1357 (100%)	1361 (100%)	1358 (100%)	4076 (100%)	836 (61.61%)	856 (62.69%)	847 (62.37%)	2539 (62.29%)
Excluded from safety population					521 (38.39%)	505 (37.11%)	511 (37.63%)	1537 (37.71%)
Reasons for exclusion from safety population								
Not dosed					521	505	511	1537
Modified Intent-to-treat (mITT) Population	806 (59.4%)	835 (61.35%)	824 (60.68%)	2465 (60.48)	836 (61.61%)	856 (62.69%)	847 (62.37%)	2539 (62.29%)
Excluded from mITT population	551 (40.6%)	526 (38.65%)	534 (39.32%)	1611 (39.52%)	521 (38.39%)	505 (37.11%)	511 (37.63%)	1537 (37.71%)
Reasons for exclusion from mITT population								
Not dosed	521	505	511	1537	521	505	511	1537
Did not meet I/E criteria at Visit 2	11	7	11	29				
Missing I/E criteria at Visit 2	13	12	9	34				
No post-screening healing assessment	3	0	2	5				
Manually removed from mITT/PP population	3	2	1	6				
Per-Protocol (PP)Population	639 (47.09%)	662 (48.64%)	647 (47.64%)	1948 (47.79%)	639 (47.09%)	662 (48.64%)	647 (47.64%)	1948 (47.79%)
Excluded from PP population	718 (52.91%)	699 (51.36%)	711 (52.36%)	2128 (52.21%)	718 (52.91%)	699 (51.36%)	711 (52.36%)	2128 (52.21%)
Reasons for exclusion from PP population								
Not dosed	521	505	511	1537	521	505	511	1537
Did not meet I/E criteria at Visit 2	11	7	11	29	11	7	11	29
Missing I/E criteria at Visit 2	13	12	9	34	13	12	9	34
No post-screening healing assessment	3	0	2	5	3	0	2	5
Manually removed from mITT/PP population	3	2	1	6	3	2	1	6
PV per CRA log	3	5	3	11	3	5	3	11
Completed/discontinued study and did not assess lesion healing	2	2	2	6	2	2	2	6
Did not have investigator healing assessment within +2 days of subject-reported healing time	48	43	57	148	48	43	57	148
Did not have visit 2 assessment within +2 days of first treatment	27	19	27	73	27	19	27	73
Did not meet study medication compliance criteria	25	34	25	84	25	34	25	84

Subject did not report healing. Investigator assessed that healing occurred but cannot determine healing time	55	53	50	158	55	53	50	158
Missed more than 5 consecutive applications of study medication	1	2	2	5	1	2	2	5
Subject reported healing, but did not include healing date/time	5	11	8	24	5	11	8	24
Subject reported healing, but investigator did not confirm healing	1	2	1	4	1	2	1	4
Prohibited medication	0	2	2	4	0	2	2	4

Source: Applicant's datasets and reviewer's analysis

Reviewer's Comment:

FDA's current definition of the mITT population is different from that of the applicant. FDA's mITT population includes all subjects who were randomized and received at least one dose of study treatment. In this case, this definition is same as the definition of the FDA's safety population.

3.1.8 Demographics and Baseline Characteristics

A summary of demographic characteristics (gender, race and age) for the FDA's mITT population is presented in Table 3 and that in the per-protocol population is presented in Table 4. Approximately 68% subjects were male in both FDA's mITT and PP populations. Majority of the subjects were white (78.53% in FDA's mITT population and 79.93% in the PP population), followed by black (19.38% in FDA's mITT population and 17.86% in the PP population). The age range was 12 to 87 years in FDA's mITT population and 12 to 85 years in the PP population. The average and median ages were 43.94 and 44 years, respectively, in FDA's mITT population and 44.03 and 44 years, respectively, in the PP population. There were 95study sites, all in USA. The enrollment per site varied from 2 to 198. Gender and age were balanced between treatment arms, but there was a larger proportion of white and smaller proportion of black in the vehicle arm than in others arms.

Table 3: Demographics in FDA's mITT Population

		Test (N=836)	Reference (N=856)	Vehicle (N=847)	All (N=2539)
Gender	Female	575 (68.78%)	575 (67.17%)	574 (67.77%)	1724 (67.90%)
	Male	261 (31.22%)	281 (32.83%)	273 (32.23%)	815 (32.10%)
Race	White	639 (76.44%)	660 (77.10%)	695 (82.05%)	1994 (78.53%)
	Black	177 (21.17%)	181 (21.14%)	134 (15.82%)	492 (19.38%)
	Asian	7 (0.84%)	3 (0.35%)	2 (0.24%)	12 (0.47%)
	American Indian or AlaskaNative	3 (0.36%)	2 (0.23%)	3 (0.35%)	8 (0.32%)
	Native Hawaiian or other pacific islander	1 (0.12%)	2 (0.23%)	1 (0.12%)	4 (0.16%)
	Other	9 (1.08%)	8 (0.93%)	12 (1.42%)	29 (1.14%)
Age in Years	Mean, SD	44.10, 14.73	44.47, 15.16	43.26, 14.79	43.94, 14.90
	Min, Max	12, 87	12, 85	12, 84	12, 87
	Q1, Median, Q3	33, 44, 55	32, 44, 55	31, 44, 54	32, 44, 54

Source: Reviewer's analysis

Table 4: Demographics in the PP Population

		Test (N=639)	Reference (N=662)	Vehicle (N=647)	All (N=1948)
Gender	Female	433 (67.76%)	444 (67.07%)	445 (68.78%)	1322 (67.86%)
	Male	206 (32.24%)	218 (32.93%)	202 (31.22%)	626 (32.14%)
Race	White	497 (77.78%)	520 (78.55%)	540 (83.46%)	1557 (79.93%)
	Black	126 (19.72%)	130 (19.64%)	92 (14.22%)	348 (17.86%)
	Asian	5 (0.78%)	3 (0.45%)	2 (0.31%)	10 (0.51%)
	American Indian or Alaska Native	3 (0.47%)	2 (0.30%)	3 (0.46%)	8 (0.41%)
	Native Hawaiian or other pacific islander	0 (0.00%)	2 (0.30%)	1 (0.15%)	3 (0.15%)
	Other	8 (1.25%)	5 (0.76%)	9 (1.39%)	22 (1.13%)
Age in Years	Mean, SD	44.09, 14.91	44.57, 15.20	43.43, 14.90	44.03, 15.00
	Min, Max	12, 85	12, 85	12, 84	12, 85
	Q1, Median, Q3	32, 44, 55	33, 44, 55	32, 44, 54	32, 44, 54

Source: Reviewer's analysis

3.1.9 Applicant's Analysis Results

The primary efficacy endpoint was the time-to-complete healing. The applicant's results of the equivalence analysis of the primary efficacy endpoint are shown in Table 7. In the PP population, the test to reference ratio of the LS means was 0.99 with a 90% CI of 0.92, 1.06. The test product was considered therapeutically equivalent to the reference product because the 90% CI of ratio of LS means fell within the interval 0.80 to 1.25. Similar results were obtained in the supportive analysis for bioequivalence using the mITT population. The T/R ratio of the LS means is 1.01 with a 90% CI of 0.93, 1.09.

Table 5: Applicant's Equivalence Analysis of the Primary Efficacy Endpoint

	Test	**Reference**
Per-Protocol (PP) Population		
Number of Subjects	639	662
Mean (SD)	107.57 (80.599)	109.71 (82.807)
LS means (SE)	104.81 (3.129)	106.34 (3.065)
Ratio of LS means (Test/Reference)	0.99	
90% confidence interval	(0.92,1.06)	
Modified Intent-to-Treat (mITT) Population		
Number of Subjects	806	835
Mean (SD)	145.61 (138.636)	146.40 (140.164)
LS means (SE)	141.16 (5.060)	140.18 (5.042)
Ratio of LS means (Test/Reference)	1.01	
90% confidence interval	(0.93, 1.09)	

Source: Clinical Study Report, Table 11-4

The applicant's results of the superiority analysis of the primary efficacy endpoint are shown in Table 8. Neither of the active treatments demonstrated significant superiority ($p<0.05$) over the vehicle control in mean time to complete healing in the mITT population ($p=0.8288$ for test product and $p=0.6945$ for reference product) and PP population ($p=0.1946$ for test product and $p=0.4000$ for reference product). The applicant noted that superiority of the test and reference products over vehicle was not demonstrated, potentially due to the nature of this self-limiting condition, subjectivity of endpoints, and large subset of non-compliance within the mITT analysis population.

Table 6: Applicant's Superiority Analysis of the Primary Efficacy Endpoint

	Test	Reference	Vehicle
Modified Intent-to-Treat (mITT) Population			
Number of Subjects	806	835	824
Mean (SD)	145.61 (138.636)	146.40 (140.164)	147.28 (136.909)
LS means (SE)	141.57 (4.870)	140.44 (4.838)	142.97 (4.860)
Comparison with Vehicle			
Difference in LS means (SE)	-1.40 (6.494)	-2.53 (6.434)	
95% confidence interval	(-14.14,11.33)	(-15.14,10.09)	
P-value	0.8288	0.6945	
Per-Protocol (PP) Population			
Number of Subjects	639	662	647
Mean (SD)	107.57 (80.599)	109.71 (82.807)	112.05 (83.343)
LS means (SE)	104.24 (3.031)	106.13 (2.974)	109.52 (3.026)
Comparison with Vehicle			
Difference in LS means (SE)	-5.28 (4.068)	-3.38 (4.021)	
95% confidence interval	(-13.26,2.70)	(-11.27,4.50)	
P-value	0.1946	0.4000	

Source: Clinical Study Report, Table 11-5

3.1.10 Reviewer's Assessments

Subjects were considered compliant if they applied at least 75% and not more than 125% of doses (15 to 25 applications), did not miss more than five consecutive applications of study medication and completed the evaluation within the designated visit window. Dosing compliance results are shown in Table 5.

Table 7: Dosing Compliance in FDA's mITT population

	Test	Reference	Vehicle	All
Applied at least 75% and no more than 125% doses	791	803	810	2404
Did not miss more than five consecutive doses	804	818	823	2445
Both of the above	790	801	808	2399

Source: Reviewer's analysis

3.1.10.1 Reviewer's Primary Analyses

The reviewer's primary analysis of equivalence comparing the mean time to complete healing between the test and reference arms in the PP population uses analysis of variance (ANOVA) with treatment and center as fixed effects. The 90% CI for the ratio (T/R) of mean time to complete healing obtained by Fieller's method is presented in Table 8.

In the FDA's PP population, the test to reference ratio of LS means of time to complete healing is 0.98 with a 90% confidence interval (0.92, 1.05). Since this 90% confidence interval falls completely inside (0.80, 1.25), equivalence of the test and reference products is established.

Table 8: Reviewer's Primary Equivalence Analysis of Time to Complete Healing in the PP Population

	Test	Reference
Number of Subjects	639	662
Mean (SD)	107.57 (80.599)	109.71 (82.807)
LS means (SE)	105.02 (3.776)	106.75 (3.635)
Ratio of LS means (Test/Reference)	0.98	
90% confidence interval	(0.92,1.05)	

Source: Reviewer's analysis

The reviewer's superiority analyses of the primary endpoint time to complete healing comparing both the test and reference arms versus the vehicle arm in FDA's mITT population using an ANOVA with treatment and site as fixed effects are shown in Table 11. None of the test and reference products are statistically significantly better than the vehicle (two-sided p-value for test vs. vehicle is 0.8646 and that for reference vs. vehicle is 0.9864). Therefore, we can conclude that the study is not sensitive and conclusion of equivalence between test and reference products cannot be made.

Table 9: Reviewer's Superiority Analysis of Time to Complete Healing in FDA's mITT Population

	Test	Reference	Vehicle
Number of Subjects	836	856	847
Mean (SD)	152.55 (146.128)	151.82 (146.594)	150.78 (140.619)
Comparison with Vehicle			
Difference in LS means (SE)	1.14 (6.709)	0.11 (6.702)	
95% confidence interval	(-12.02,14.30)	(-13.03,13.26)	
P-value (two-sided)	0.8646	0.9864	

Source: Reviewer's analysis

3.1.10.2 Reviewer's Sensitivity Analyses

Analysis of equivalence comparing the mean time to complete healing between the test and reference arms in FDA's mITT populations uses analysis of variance (ANOVA) with treatment and center as fixed effects. The 90% CI for the ratio (T/R) of mean time to complete healing obtained by Fieller's method is presented in Table 9. The results are similar to those in the PP population.

Table 10: Reviewer's Equivalence Analysis of Time to Complete Healing in FDA's mITT Population

	Test	Reference
Number of Subjects	836	856
Mean (SD)	152.55 (146.128)	151.82 (146.594)
LS means (SE)	147.71 (6.590)	145.63 (6.504)
Ratio of LS means (Test/Reference)	1.01	
90% confidence interval	(0.94, 1.10)	

Source: Reviewer's analysis

A total of 358 subjects (112 in the test arm, 126 in the reference arm and 120 in the vehicle arm) did not experience any lesion outbreak, i.e., experienced an "aborted lesion". The applicant assigned a value of zero for the primary endpoint, time to complete healing, if the subject experienced an aborted lesion. The review team had a concern that assigning a value of zero for time to complete healing for the subjects with an aborted lesion made the average time to complete healing smaller than they actually are. To address this issue, the reviewer performed equivalence analyses in both FDA's PP and mITT populations excluding the subjects who had an aborted lesion. The results of those analyses are presented in Table 10. These results are similar to the results seen in the analyses where no subject was excluded because of aborted lesions.

Table 11: Reviewer's Equivalence Analyses of Time to Complete Healing in FDA's PP and mITT Populations Excluding Subject with Aborted Lesions

	Test	Reference
Per-Protocol (PP) Population		
Number of Subjects	534	553
Mean (SD)	128.72 (71.050)	131.34 (73.251)
LS means (SE)	123.92 (3.141)	127.43 (3.045)
Ratio of LS means (Test/Reference)	0.97	
90% confidence interval	(0.93,1.02)	
Modified Intent-to-Treat (mITT) Population		
Number of Subjects	724	730
Mean (SD)	176.15 (143.173)	178.02 (143.292)
LS means (SE)	169.30 (6.433)	168.92 (6.423)
Ratio of LS means (Test/Reference)	1.00	
90% confidence interval	(0.94, 1.07)	

Source: Reviewer's analysis

Tests of superiority of the test and reference products over vehicle in the PP population are presented in Table 13. Neither the test nor the reference product showed statistically significant superiority over the vehicle (p-values for test vs vehicle and reference vs vehicle were 0.1849 and 0.3559, respectively.

Table 12: Reviewer's Superiority Analysis of Time to Complete Healing in the PP Population

	Test	Reference	Vehicle
Number of Subjects	639	662	647
Mean (SD)	107.57 (80.599)	109.71 (82.807)	112.05 (83.343)
Comparison with Vehicle			
Difference in LS means (SE)	-5.43 (4.093)	-3.73 (4.035)	
95% confidence interval	(-13.46,2.60)	(-11.64,4.19)	
P-value (two-sided)	0.1849	0.3559	

Source: Reviewer's analysis

The reviewer's analyses of superiority excluding the subjects who experienced an aborted lesion are presented in Table 13. Only in the PP population excluding the subjects with aborted lesions, the test showed significant superiority over vehicle (two-sided p-value: 0.0358). All other comparisons failed to show statistically significant superiority of test or reference over vehicle.

Table 13: Reviewer's Superiority Analysis of Time to Complete Healing in FDA's PP and mITT Populations Excluding Subject with Aborted Lesions

	Test	Reference	Vehicle
Modified Intent-to-Treat (mITT) Population			
Number of Subjects	724	730	727
Mean (SD)	176.15 (143.173)	178.02 (143.292)	175.66 (136.617)
Comparison with Vehicle			
Difference in LS means (SE)	-1.31 (6.775)	-0.01 (6.887)	
95% confidence interval	(-14.60,11.98)	(-13.52,13.51)	
P-value (two-sided)	0.8468	0.9993	
Per-Protocol (PP) Population			
Number of Subjects	534	553	536
Mean (SD)	128.72 (71.050)	131.34 (73.251)	135.25 (72.409)
Comparison with Vehicle			
Difference in LS means	-7.48 (3.555)	-5.17 (3.471)	
95% confidence interval	(-14.45,-0.50)	(-11.98,1.64)	
P-value (two-sided)	0.0358	0.1356	

Source: Reviewer's analysis

3.1.10.3 Additional Analyses

The reviewer also performed survival analysis of time to complete healing in the FDA's PP and mITT populations. The Kaplan-Meier plots of time to complete healing in FDA's PP and mITT populations are presented in Figure 1 and Figure 2, respectively. Based on Cox proportional hazards model, the hazard ratios along with their 95% confidence intervals for the pairwise comparisons of time to complete healing in different treatment arms in both FDA's mITT and PP

populations are presented in Table 14. Test, reference and vehicle do not show significant difference between one another in time to complete healing.

Table 14: Hazard Ratios and Confidence Intervals for Pairwise Comparisons of Time to Complete Healing

Population	Comparison	Hazard Ratio	95% Confidence Interval for Hazard Ratio
FDA's PP	Test vs. Reference	0.960	(0.852, 1.082)
	Test vs. Vehicle	0.959	(0.903, 1.018)
	Reference vs. Vehicle	0.955	(0.848, 1.076)
FDA's mITT	Test vs. Reference	0.984	(0.881, 1.099)
	Test vs. Vehicle	0.997	(0.943, 1.053)
	Reference vs. Vehicle	1.009	(0.904, 1.127)

Source: Reviewer's analysis

Figure 1: Kaplan-Meier Plot of Time to Complete Healing in the PP Population

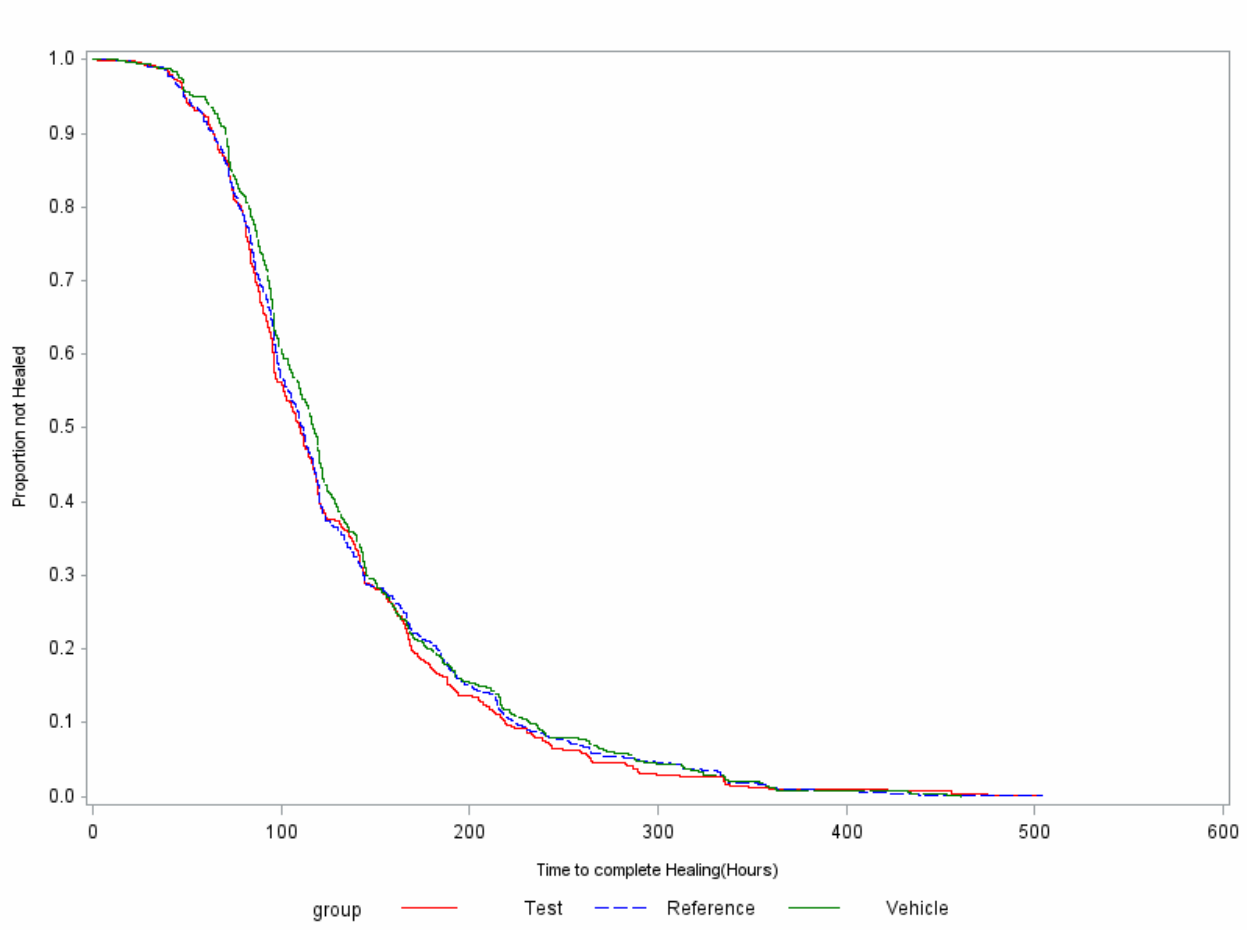
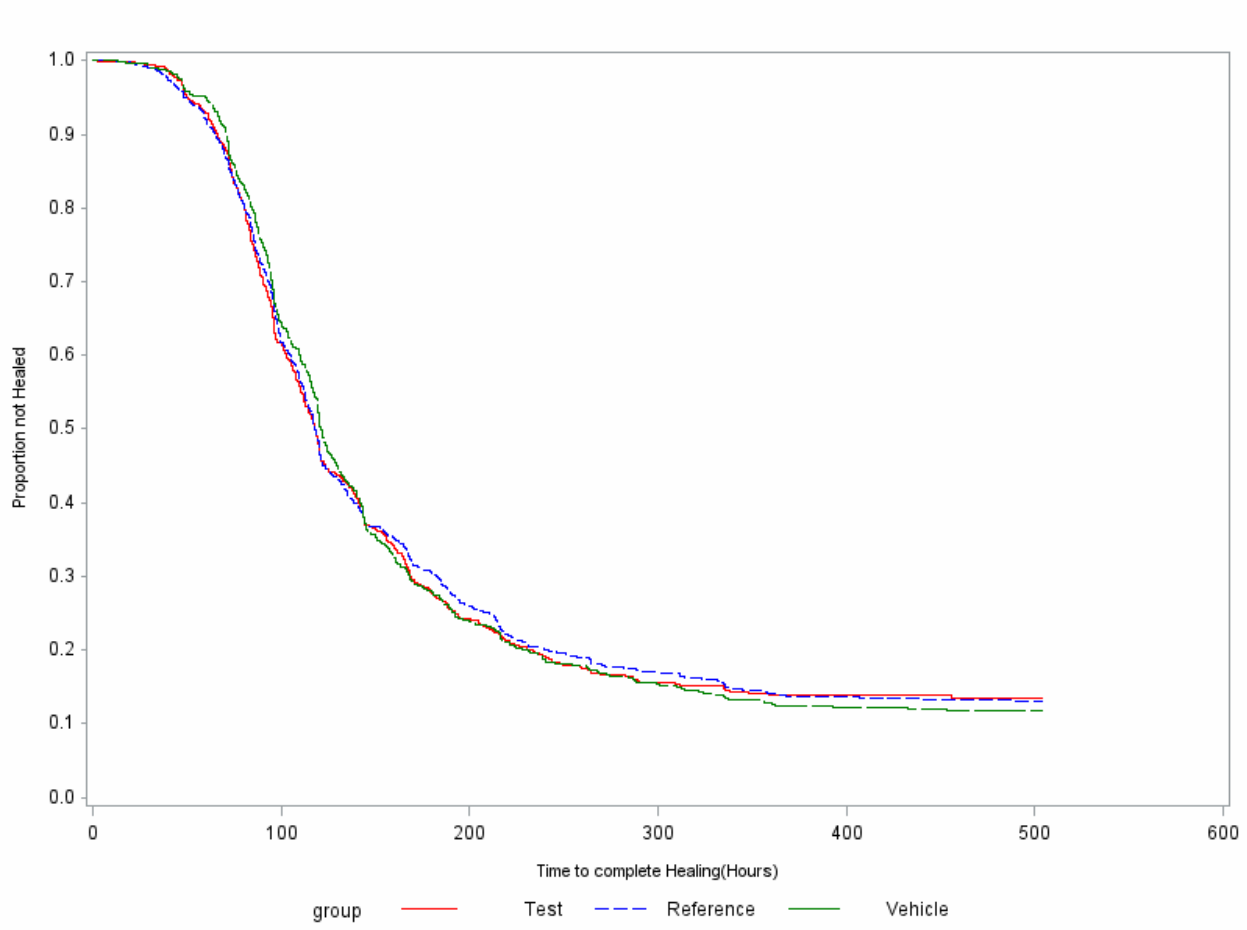


Figure 2: Kaplan-Meier Plot of Time to Complete Healing in FDA's mITT Population



4 SUMMMARY AND CONCLUSIONS

4.1 Side by Side Tables for DCR Reviewers

Table 15: Applicant's and FDA's Determination of Analysis Populations

	Applicant's Determination				FDA's Determination			
	Test	Reference	Vehicle	All	Test	Reference	Vehicle	All
Enrolled (randomized)	1357	1361	1358	4076	1357	1361	1358	4076
Safety Population	1357 (100%)	1361 (100%)	1358 (100%)	4076 (100%)	836 (61.61%)	856 (62.69%)	847 (62.37%)	2539 (62.29%)
Excluded from safety population					521 (38.39%)	505 (37.11%)	511 (37.63%)	1537 (37.71%)
Reasons for exclusion from safety population								
Not dosed					521	505	511	1537
Modified Intent-to-treat (mITT) Population	806 (59.4%)	835 (61.35%)	824 (60.68%)	2465 (60.48)	836 (61.61%)	856 (62.69%)	847 (62.37%)	2539 (62.29%)
Excluded from mITT population	551 (40.6%)	526 (38.65%)	534 (39.32%)	1611 (39.52%)	521 (38.39%)	505 (37.11%)	511 (37.63%)	1537 (37.71%)
Reasons for exclusion from mITT population								
Not dosed	521	505	511	1537	521	505	511	1537
Did not meet I/E criteria at Visit 2	11	7	11	29				
Missing I/E criteria at Visit 2	13	12	9	34				
No post-screening healing assessment	3	0	2	5				
Manually removed from mITT/PP population	3	2	1	6				
Per-Protocol (PP)Population	639 (47.09%)	662 (48.64%)	647 (47.64%)	1948 (47.79%)	639 (47.09%)	662 (48.64%)	647 (47.64%)	1948 (47.79%)
Excluded from PP population	718 (52.91%)	699 (51.36%)	711 (52.36%)	2128 (52.21%)	718 (52.91%)	699 (51.36%)	711 (52.36%)	2128 (52.21%)
Reasons for exclusion from PP population								
Not dosed	521	505	511	1537	521	505	511	1537
Did not meet I/E criteria at Visit 2	11	7	11	29	11	7	11	29
Missing I/E criteria at Visit 2	13	12	9	34	13	12	9	34
No post-screening healing assessment	3	0	2	5	3	0	2	5
Manually removed from mITT/PP population	3	2	1	6	3	2	1	6
PV per CRA log	3	5	3	11	3	5	3	11
Completed/discontinued study and did not assess lesion healing	2	2	2	6	2	2	2	6
Did not have investigator healing assessment within +2 days of subject-reported healing time	48	43	57	148	48	43	57	148

Did not have visit 2 assessment within +2 days of first treatment	27	19	27	73	27	19	27	73
Did not meet study medication compliance criteria	25	34	25	84	25	34	25	84
Subject did not report healing. Investigator assessed that healing occurred but cannot determine healing time	55	53	50	158	55	53	50	158
Missed more than 5 consecutive applications of study medication	1	2	2	5	1	2	2	5
Subject reported healing, but did not include healing date/time	5	11	8	24	5	11	8	24
Subject reported healing, but investigator did not confirm healing	1	2	1	4	1	2	1	4
Prohibited medication	0	2	2	4	0	2	2	4

Source: Applicant's datasets and reviewer's analysis

Table 16: Primary Endpoint Analysis per Applicant and FDA

	Applicant's Analysis			FDA's Analysis		
	Test	**Reference**	**Vehicle**	**Test**	**Reference**	**Vehicle**
Per-Protocol (PP) Population						
Number of Subjects	639	662	647	639	662	647
Mean (SD) of time to complete healing	107.57 (80.599)	109.71 (82.807)	112.05 (83.343)	107.57 (80.599)	109.71 (82.807)	112.05 (83.343)
Ratio of LS means (Test/Reference)	0.99			0.98		
90% confidence interval of ratio[1]	(0.92,1.06)			(0.92,1.05)		
Is 90% CI within (0.80, 1.25)?	Yes			Yes		
Modified Intent-to-Treat (mITT) Population[3]						
Number of Subjects	806	835	824	836	856	847
Mean (SD) of time to complete healing	145.61 (138.636)	146.40 (140.164)	147.28 (136.909)	152.55 (146.128)	151.82 (146.594)	150.78 (140.619)
Comparison with Vehicle						
Difference of LS mean time to complete healing (SE)	-1.40 (6.494)	-2.53 (6.434)		1.14 (6.709)	0.11 (6.702)	
95% Confidence Interval for Test-Reference	(-14.14, 11.33)	(-15.14, 10.09)		(-12.02, 14.30)	(-13.03, 13.26)	
P -value[2] for Superiority Test Against Vehicle	0.8288	0.6945		0.8646	0.9864	

[1]: Using Fieller's method. [2]: Based on an ANOVA model with treatment and site as fixed effects. [3]: FDA's mITT population differs from that of the applicant.

4.2 Statistical Issues

1. The test and reference products showed equivalence. However, both test and reference products failed to show statistically significant superiority over vehicle. Therefore the study does not have assay sensitivity and cannot be used to establish bioequivalence.

2. The applicant's definition of the primary endpoint matches with the recommended primary endpoint, the duration of episode (DOE), in FDA's Draft Guidance on Acyclovir for subjects who experience a vesicular lesion. For subjects whose primary lesion was not vesicular, the draft guidance recommends DOE to be defined as the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last. However, the applicant did not provide any definition of time to complete healing in the case of non-vesicular primary lesion. The applicant censored the subjects with non-vesicular lesions at time 0 (time of first dosing).

3. The applicant used the same definition for the safety and ITT populations. The definition is consistent with the generally used definition for the ITT population but not the safety population. The subjects should have taken at least one dose of study medication to be included in the safety population and should be classified as treated, not as randomized.

4. FDA's current definition of the mITT population is different from that of the applicant. FDA's mITT population includes all subjects who were randomized and received at least one dose of study treatment. In this case, this definition is same as the definition of the FDA's safety population.

4.3 Conclusions and Recommendations

The applicant has submitted results from one multicenter, randomized, double-blind, vehicle-controlled, parallel group study to compare the test product Acyclovir cream, 5% (Perrigo) and the reference product Zovirax (acyclovir) cream 5% (Valeant Pharmaceuticals) for the treatment of recurrent herpes labialis. The test and reference products showed equivalence with respect to time to complete healing in the per-protocol (PP) population. However, both test and reference products failed to show statistically significant superiority over the vehicle cream with respect to time to complete healing in the FDA's modified intent-to-treat (mITT) population. The study lacked assay sensitivity. Therefore, bioequivalence between the test and reference products cannot be established. This study in isolation has major deficiency based on the statistical results. The evaluation of the application would depend on the clinical considerations and justifications by FDA's clinical review team in the Division of Clinical Review based on the totality of the evidence. The statistical team defers the review recommendation to the FDA's clinical team.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

OTHER REVIEW(s)

Clinical Bioequivalence Review
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

ANDA number	**208702**
Drug Product	Acyclovir Cream
Strength	5%
Applicant Name	Perrigo UK FINCO Limited Partnership's (Perrigo)
Treatment Indication	Recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older
Reference Listed Drug (RLD)	Zovirax® (acyclovir) Cream, 5%
NDA number for RLD	021478
RLD Sponsor Name	Valeant International Bermuda
ANDA Submission Dates	Original Submission: 01/07/2016 (IVRT) Amendments: • In vitro Release Testing (IVRT): 03/02/2016, 04/05/2016, 06/01/2016, and 02/09/2017 • Clinical endpoint BE Study (Unsolicited Major Amendment): 04/05/2018
Materials Reviewed	1) ANDA Submission 04/05/2018 (Unsolicited Major Amendment) 2) Clinical/Response to Information Request (IR) 07/19/2018 3) Clinical/Response to IR 07/24/2018 4) Clinical Response to IR 08/23/2018 5) FDA Product-Specific Guidance: Recommended December 2015; Revised December 2016 6) FDA Statistical Review by Somesh Chattopadhyay, PhD completed 09/27/2018 7) FDA OSIS Bioequivalence Audit Request 04/11/2018): OSIS Establishment Inspection Report (EIR) by Mohsen Rajabi Abhari, PhD dated 11/30/2018
Primary Reviewer	Raquel Tapia, MD Medical Officer
Secondary Reviewer	Carol Kim, PharmD Acting Team Leader, ANDA Team
Tertiary Reviewer	Sarah Yim, MD Division Director
Date of Completion	01/24/2019
GDUFA Goal Date	02/04/2019
DCR Conclusion	DCR recommends approval of this application. Despite insufficient assay sensitivity to definitively demonstrate BE on its own, the overall results of Study PRG-NY-14-008, including comparable clinical response between the test and the reference product and no safety concerns, are adequate to provide the biorelevant information ordinarily provided by the in vitro permeation data (IVPT). Thus, Study PRG-NY-14-008 can support the available acceptable data for the in vitro BE approach for the proposed formulation, which is Q1/Q2/Q3 the same to the RLD with acceptable in vitro release testing (IVRT) data. Therefore, based on the totality of information in the application, DCR concludes the proposed generic would likely be therapeutically equivalent to and substitutable for the RLD.
Deficiency Classification	☐ Major (Deficiencies to be communicated by CR) ☐ Minor ☒ N/A (Review is Adequate)

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1 EXECUTIVE SUMMARY

1.1 Approval Recommendation

Based on the totality of information in this application, the Division of Clinical Review (DCR) recommends approval. Although clinical endpoint bioequivalence (BE) study PRG-NY-14-008 did not have sufficient assay sensitivity to definitively conclude BE because statistically significant superiority of Test and Reference Listed Drug (RLD) was not demonstrated over vehicle treatment alone, this is likely due to limited treatment effect size of the RLD. A vehicle effect was noted in the original reviews of the RLD and was postulated as a factor in the limited treatment effect size. As the purpose of the superiority to placebo/vehicle is to only to confirm assay sensitivity of the study (i.e. that Test and RLD are BE in a study able to show a treatment effect), having a placebo/vehicle that has an effect on its own would make this endeavor more difficult, and for endpoints with such a small treatment effect size, perhaps a true placebo should be considered, if clinically feasible. In any case, the Test and RLD did appear to show a response, albeit not large enough over the vehicle to be statistically significant; and descriptive results from the study support a comparable clinical response between Test and RLD and do not raise any clinical concerns.

Although the clinical data is not adequate on its own to definitively conclude BE, in this case it is not on its own, as the application was originally submitted with an in vitro approach. That makes this case unique in that, in addition to the clinical data, the proposed formulation is qualitatively (Q1), quantitatively (Q2) the same as the RLD, with comparable physicochemical characterization (Q3) and demonstrates acceptable in vitro release (IVRT) performance. Acknowledging that the in vitro approach would ordinarily be considered incomplete without adequate in vitro permeation test (IVPT) data, IVPT is performed as a biorelevant performance test to support BE, and the in vitro approach is ordinarily done as an alternative to a clinical endpoint BE study, so there would not ordinarily be clinical data. In this case, the clinical data from Study PRG-NY-14-008 represents an extensive therapeutic experience that provides more direct information than IVPT on the clinical performance of the formulation and mitigates the remaining uncertainty in this application's in vitro approach. Our recommendation further takes into consideration the context of use and risk-benefit profile of the RLD. Therefore, based on these global considerations and totality of information in the application, DCR concludes the Test and RLD are likely to be therapeutically equivalent and substitutable, and recommends approval of ANDA 208702.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

This review evaluates the clinical endpoint BE study data submitted in abbreviated new drug application (ANDA) 208702 on 04/05/2018 to determine the bioequivalence of Perrigo UK FINCO Limited Partnership's (the Applicant) Acyclovir Cream, 5 % with the RLD, Valeant International Bermuda's Zovirax® (acyclovir) Cream, 5%, NDA 021478 approved on 12/30/2002. In support of approval of the ANDA, the Applicant conducted in vitro studies, reviewed by the Division of Bioequivalence (DB) and Division of Therapeutic Performance (DTP), and a clinical endpoint BE study (Study PRG-NY-14-008) in 4,076 subjects with recurrent herpes simplex labialis (RHL), reviewed by DCR.

1.2.2 Comparative Efficacy

Per FDA draft product-specific guidance (PSG) for acyclovir cream, recommended in December 2014 (revised December 2016), one of two approaches, i.e., in vitro studies or an in-vivo clinical endpoint study, is recommended to establish BE to Zovirax (acyclovir) Cream 5%. In the in vivo option, the guidance anticipates that a relatively large number of subjects would need to be enrolled for a clinical endpoint study given modest efficacy demonstrated in the clinical trials of the RLD. Consistent with this guidance, the submitted clinical endpoint study, Study PRG-NY-14-008, was a multicenter (all US sites, 97), randomized, double blind, parallel-group, vehicle-controlled study in 4,076 immunocompetent males and females, with a clinical diagnosis of non–life-threatening RHL. The overall study design of Study PRG-NY-14-008 is consistent with the recommendations outlined in the guidance, except for age requirement for enrollment, i.e., 18 years or older in the PSG vs. ≥12 years in Study PRG-NY-14-008; and clinical endpoints, i.e., the draft acyclovir PSG defines clinical endpoints for both vesicular and nonvesicular (aborted) lesion, but PRG-NY-14-008 defines clinical endpoints for vesicular lesions only.

Per study design, subjects were randomized in a 1:1:1 ratio to receive one of three treatments (test, RLD, vehicle). The subjects received the study drugs at the time of screening (Visit 1) and received instructions to apply the study drug product upon first symptoms of a recurrence, i.e., within 1 hour of the signs or symptoms (prodrome) and before the clinical sign of a cold sore (blister), and continue applications five times a day for 4 days (regardless of healing status). Subjects were also instructed to return to the study clinic for Visit 2 (Day 1 of treatment) within 24 hours of treatment initiation. Follow-ups were planned as daily for 3 days [Visit 3 (Day 2), Visit 4 (Day 3), and Visit 5 (Day 4)] with study medications to be returned on Day 5 (visit 6). Subjects whose lesions had healed prior to Day 5, Day 5 was still their End of Study visit. Otherwise, follow up visits were planned for Days 6, 7, 8, 10, 12, 14, and 21 for subjects who did not heal prior to Day 5.

The primary efficacy endpoint was time to complete healing of lesion, defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator based on both clinical observation and review of the subject's diary. Time to healing was measured in hours from the time of first dosing. In general, the current acyclovir draft PSG defines the primary endpoint as duration of episode (DOE) with two primary outcomes based on whether lesions are vesicular or nonvesicular. The PSG states, in verbatim,

> a. For subjects who experience a vesicular lesion, DOE is the time from the treatment initiation to the healing of primary lesions (loss of crust; residual erythema may be present after loss of hard crust).
>
> b. For subjects whose primary lesions were not vesicular in nature, DOE is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last.

The Applicant's definition of the primary endpoint is consistent with the acyclovir draft PSG for vesicular lesions, but no definition of time to complete healing for subjects with non-vesicular lesions was provided; these subjects were assigned a value of "0" for the primary endpoint outcome variable.

A total of 4,076 subjects were randomized from 10/06/2014 to 04/27/2016: 1,357 subjects to the test arm, 1,361 subjects to the reference arm and 1,358 subjects to the vehicle arm. Among them, 1,537 subjects were not dosed and were never exposed to the study drug while 2,416 subjects (793 in the test, 810 in the reference, and 813 in the vehicle) completed the study. Of the 1,537 subjects not dosed, 669 (16.41%) did not experience recurrence.

Of the 4,076 subjects enrolled, 2,539 were included in the FDA modified intent-to-treat (mITT) population and 1,948 subjects in the per- protocol (PP) population. Both FDA and Applicant's PP populations were the same; the mITT population differed by 74 subjects excluded from the Applicant's mITT population, but not the FDA's. Primary evaluation of bioequivalence was determined using the PP population by comparing the time to complete healing in each treatment group.

According to the Applicant and FDA statistical analyses, the results in the PP populations showed equivalence between the test product and the RLD for the primary endpoint. The mean time to healing in the PP population was 107.57 hours in the test group vs. 109.71 hours in the RLD group and the test to reference ratio of Least Square (LS) means of time to complete healing was 0.98, which fell within the 90% confidence interval BE parameters (0.92, 1.05), which is within the acceptable BE limits of [0.80, 1.25]. However, for the demonstration of assay sensitivity (the part of the study that tests whether the study is adequately sensitive to detect a difference between groups if a difference exists), the test and RLD groups were not individually statistically superior at the 5% significance level compared to the placebo for the primary endpoint in the Applicant and FDA mITT population analyses, even with post-hoc exclusion of subjects with nonvesicular lesions. The Applicant's justification for failing superiority includes the self-limiting nature of herpes labialis, subjectivity of endpoints, and large subset of noncompliance within the mITT analysis population.

DCR considers other potential reasons to explain the failed superiority testing in this study as follows:

1. Only modest efficacy was demonstrated in the clinical trials of the RLD, postulated to be due to the self-limited nature of RHL and a possible vehicle effect, as the vehicle groups had a shorter recovery time than expected based on historical experience.
2. Given that enrollment was based on clinical diagnosis alone (without virologic confirmation), the HSV-infected population is likely diluted, which further limits the ability to detect efficacy differences among the treatment groups.

The OSIS inspection report, dated 11/30/2018, concluded that the data from the audited study PRG-NY-14-008 are reliable and recommends that data from the study be accepted for Agency review.

Study PRG-NY-14-008 was submitted by the applicant to support their in vitro BE approach. In addition to Test and RLD being qualitatively (Q1) and quantitatively (Q2) the same[1] with

[1] ANDA208702 Acyclovir Cream DB review by Li Li, PhD uploaded in GDRP 07/10/2018
http://panorama.fda.gov/document/view?ID=5b339d4d00756de7f913d61d490ff574

comparable physicochemical properties (Q3)[2], the PSG of this product recommends in vitro release test (IVRT) data to demonstrate equivalent rate of acyclovir release, and in vitro permeation test (IVPT) data to support BE. In this case, the applicant provided an in vitro approach that included acceptable IVRT result but inadequate IVPT data.[3] Although the clinical data from Study PRG-NY-14-008 is not adequate on its own to definitively conclude BE, the data represent an extensive clinical therapeutic experience that helps to mitigate the remaining uncertainty from the IVPT data, because the IVPT data is intended to serve as a biorelevant performance test whereas Study PRG-NY-14-008 provides direct information on clinical performance. As stated in the Executive Summary, based on global considerations and the totality of the information in the application, DCR believes there is adequate information to conclude that the products will be therapeutically equivalent and substitutable.

1.2.3 Comparative Safety

Of the 4,076 subjects, 1,537 were not dosed. Originally, the Applicant did not exclude these subjects from the safety population, which is not consistent with the generally used definition for the safety population that subjects should have taken at least one dose of the study drug. Thus, DCR requested the Applicant to reanalyze the data excluding subjects who were not exposed to the study drugs. The Applicant resubmitted the data excluding subjects who were not dosed (1,537 subjects). At such, 2,539 subjects who applied the study drugs conformed the safety population: 836 subjects in the test group, 856 subjects in the reference group, and 847 subjects in the vehicle group. A total of 141 subjects reported 169 adverse events (AE). Most AEs were mild (85 subjects) or moderate (50 subjects) in nature. Two subjects (0.2%) in the test product group and 4 subjects (0.5%) in the reference product group experienced treatment-emergent SAEs. These SAEs were atrial fibrillation and thyroid cancer in the test group and forearm fracture, dehydration, nephrolithiasis, and hypertension in the reference product group. In addition, a subject in the test product group experienced a non-treatment emergent (colon cancer) AE). None of these SAEs were considered related to study drugs; there were no deaths in this study.

Application site reactions (burning, cracked lips, desquamation, dry lips, dryness of skin, flakiness of skin, pruritus, and stinging of the skin) were assessed at each visit as part of the herpes lesion assessment and were considered AE only if they warranted temporary discontinuation of the study drug. As an AE, each application site reaction occurred in less than 1% per treatment arm consistent with application sire reactions observe in the RLD. Per RLD labeling, acyclovir has irritation and contact sensitization potential. This was not observed in the study. Based on the formulation sameness between products, there is low expectation that there would be a difference in irritation and contact sensitization potentials between products.

Overall, Study PRG-NY-14-008 showed no concerning clinical differences in the safety profile between the RLD and the proposed test formulation; the frequency and nature of AEs are comparable among the treatment groups. The SAEs reported and the AEs leading to study drug

[2] ANDA208702 Acyclovir Quality Review by Filita Moore, uploaded in GDRP 03/16/2017 http://panorama.fda.gov/document/view?versionID=58cac74101e97f40d33c09ae04526475

[3] ANDA208702 Acyclovir Cream 5% DTP review entered in GDRP by Sameersingh (Sam) Raney, PhD http://panorama.fda.gov/document/preview?versionID=5afa1daa003466c1410b3e0978f675c1&ID=5af34963001e133e8afc4b56dd4b4c9b

interruption or discontinuation were unlikely related to the study drugs.

2 CLINICAL REVIEW

2.1 Introduction and Background

2.1.1 Summary of Drug Information

Reference Listed Drug	Zovirax® (acyclovir) Topical Cream, 5%
RLD Sponsor Name	Valeant International Bermuda (VIB)
RLD NDA/ANDA Number	NDA 021478
Date of RLD Approval	12/30/2002
Current Label	Current label was approved on 04/01/2014 under NDA 021478/S-007 https://elist fda.gov/prpllr/public/spl/4a1d6fe3-50c8-480b-ba41-4551e136943c/4a1d6fe3-50c8-480b-ba41-4551e136943c.view
Approved Indication(s)	Zovirax Cream 5% is a herpes simplex virus (HSV) nucleoside analogue DNA polymerase inhibitor indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older
Recommended Dose/Administration	Zovirax Cream should be applied 5 times per day for 4 days. Therapy should be initiated as early as possible following the onset of signs or symptoms of herpes labialis, i.e., during the prodrome or when lesions appear. For adolescents 12 years of age and older, the dosage is the same as in adults.
Boxed Warnings	There is no boxed warning
Commonly reported Adverse Events	In clinical trials, the most common adverse reactions at the site of topical application were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; each adverse reaction occurred in less than 1% of patients receiving Zovirax Cream and placebo. Postmarketing: angioedema, anaphylaxis (general) and contact dermatitis, eczema (skin)
Contraindications	Patients with known hypersensitivity to acyclovir, valacyclovir, or any component of the formulation
Prominent Warnings/ Precautions	○ Contact sensitization: Zovirax Cream has a potential for irritation and contact sensitization ○ Application to human mucous membranes (eye or inside the mouth or nose) is not recommended ○ Cream should only be applied on the affected external aspects of the lips and face in patients with herpes labialis
Mechanism of Action	Acyclovir is an antiviral drug active against herpes simplex virus (herpes simplex virus (HSV) nucleoside analogue DNA polymerase inhibitor)
Absorption	Systemic absorption of acyclovir from Zovirax Cream is minimal in adults. The systemic absorption of acyclovir following topical application of cream has not been evaluated in patients <18 years of age.

Reviewer Comments:

1. *Acyclovir is recommended for patient 12 years and older.*
2. *Systemic absorption is minimal.*
3. *Application site reactions occurred in less than 1% patients.*
4. *Topical acyclovir has the potential for contact sensitization and irritation.*

2.1.2 Regulatory Background

Perrigo UK Finco Ltd Partnership submitted ANDA 208702 for acyclovir cream, 5% on 01/07/2016. The reference listed drug (RLD) is Valeant International Bermuda's Zovirax® (acyclovir) Topical Cream, 5% (NDA 021478) approved on 12/30/2002.

In the original submission, the Perrigo requested waiver of in vivo bioequivalence (BE) studies and submitted 1) comparative physicochemical characterization of the test and RLD formulations; 2) comparative in vitro drug release test (IVRT) of acyclovir from the test and RLD formulations, and 3) comparative in vitro skin permeation test (IVPT) of acyclovir from the test and RLD formulations to support the waiver request. The Applicant received Complete Response (CR) on 03/17/2017 due to failed Q3 and deficiencies in the IVRT and IVPT methods.[4]

On 08/24/2017, Perrigo submitted 1st Major Complete Response Amendment in response to the list of deficiencies in the CR letter.[5] Per Division of Bioequivalence II (DB) review by Li Li, PhD, the proposed acyclovir formulation is Q1, Q2, and Q3 the same as the RLD and the IVRT is adequate.[6] However, a CR with in vitro major deficiency is likely because of inadequate IVPT results. Per Division of Therapeutic Performance (DTP) review by Dr. Sam Raney on 05/14/2018, IVPT is inadequate because of the following issues, in verbatim[7]

> "…the IVPT method appears to have been inadequately developed, inappropriately implemented, insufficiently qualified and validated, and inconclusively analyzed. The dataset is very small, highly variable, apparently insensitive and not even selective for acyclovir. The applicant should be recommended to develop and validate its IVPT method per the PSG and repeat the pivotal IVPT study ensuring that the IVPT study is adequately powered."

On 04/05/2018, Perrigo submitted Unsolicited Major Amendment (AMEND-06), with the results of an in vivo clinical endpoint BE study comparing the safety and efficacy of the proposed acyclovir cream, 5% (test product) to Zovirax® Cream, 5%, which is the subject of this review.

2.1.2.1 Guidance on Drug Product

Draft product specific guidance (PSG) for acyclovir cream, 5% was first recommended in December 2014 providing an in vitro and an in vivo option to demonstrate BE to Zovirax Cream, 5%. In December 2016, the PSG guidance was updated to further explain the requirements for the in vitro option to qualify for waiver of the clinical endpoint BE studies; the in vivo option

[4] ANDA208702 Acyclovir Cream Complete Response Letter Dated 03/17/2017
http://panorama.fda.gov/document/preview?versionID=58cc07e301f5dbb3356d0332528e7c85&ID=58cae09901ec84dfa0400c660f986733
[5] ANDA208702 Acyclovir Cream Complete Response Amendment -Bioequivalence Dated 08/24/2017
\\cdsesub1\evsprod\anda208702\0005\m1\us\1-2-1-cover-letter-0005.pdf
[6] ANDA208702 Acyclovir Cream DB review by Li Li, PhD uploaded in GDRP 07/10/2018
http://panorama.fda.gov/document/view?ID=5b339d4d00756de7f913d61d490ff574
[7] ANDA208702 Acyclovir Cream 5% DTP review entered in GDRP by Sameersingh (Sam) Raney, PhD
http://panorama.fda.gov/document/preview?versionID=5afa1daa003466c1410b3e0978f675c1&ID=5af34963001e133e8afc4b56dd4b4c9b

was not revised in the December 2016 draft PSG guidance. Briefly, the draft PSG for acyclovir cream, 5%, highlights four key factors that must be met in order to qualify for the in vitro option, in verbatim,

> "A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards,* Revision 1 (May 2015).
> B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.
> C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.
> D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method."

Only the in vivo option, with detailed recommendations for a clinical endpoint in vivo BE study, is relevant to this review and is summarized in Table 2.1.2.1.1 below. For full PSG details, see FDA Website Drugs@FDA:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428195.pdf

2.1.2.1.1 Drug Product Draft Guidance

Draft Guidance	Draft Guidance on Acyclovir Cream[8]
Date(s) Posted	Recommended December 2014; Revised December 2016
Recommended Study	A clinical endpoint BE study.
Clinical Endpoint Study Recommendations	**Study design:** Randomized, double blind, parallel, three-arm, placebo-controlled, in vivo study comparing the test product versus the RLD and placebo (vehicle) control. **Strength:** 5% **Subjects:** Healthy, immunocompetent adult males and non-pregnant, non-lactating females with recurrent herpes labialis (RHL). **Treatment administration/Dosing:** Treatment should be applied five times per day for 4 days (20 applications) with treatment initiated as early as possible following the onset of signs or symptoms of herpes labialis, i.e., during prodrome or no later than when herpetic lesions first appear. Within 24 hours (study Day 1) of initiating treatment with study drug, recommend that subjects return to study site for investigator assessments and return to study site for investigator assessments daily thereafter (or as often as possible) until: a. healing of the primary vesicular lesion, for those subjects who experience a vesicular lesion, OR b. return to normal skin or the cessation of symptoms, whichever occurs last, for those subjects whose primary lesions are not vesicular in nature. Provide subjects with a diary and instruct them to record their symptoms, such as pain, tenderness, tingling, itching, discomfort and the stage of their herpes lesions (normal lip, erythema, papule, vesicle, ulcer, crust), at a minimum of twice daily. **Key Inclusion Criteria:**

[8] Draft Guidance on Acyclovir Cream 5%, posted Dec 2014, revised Dec 2016
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428195.pdf

	a. Healthy, immunocompetent male or non-pregnant, non-lactating females aged at least 18 years with recurrent herpes labialis. b. At least 3 recurrences of a typical herpes labialis lesion within the past year. • At least half of recurrences preceded by recognizable prodromal symptoms, e.g., itching, redness, burning, tingling or a sense of irritation. • At least half of prodromes followed by classical lesions, e.g., ulcer, vesicle, and/or hard crust. **Primary endpoint:** The recommended primary endpoint is the duration of episode (DOE) assessed by the investigator, based on both clinical observation and review of the subject diary, and defined as: a. For subjects who experience a vesicular lesion, DOE is the time from the treatment initiation to the healing of primary lesions (loss of crust; residual erythema may be present after loss of hard crust). b. For subjects whose primary lesions were not vesicular in nature, DOE is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last. The primary endpoint is calculated by subtracting the recorded time of the first application of study medication in the case report from the recorded time of the investigator-assessed healing. The accepted PP population used for BE evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, applied a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than 1 consecutive day, and complete the evaluation within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation. **Additional comments:** Due to the modest efficacy demonstrated by the RLD, it is anticipated that a relatively large number of subjects would need to be enrolled.

Reviewer comments:

1. *Draft PSG for acyclovir cream, 5% was released in December 2014, about 2 months after Study PRG-NY-14-008 started enrolling subjects (first subject was enrolled 10/06/2014). Thus, there was no PSG for acyclovir at the time of study protocols, IRB approval or study initiation.*
2. *Despite the lack of the PSG, the overall study of Study PRG-NY-14-008, i.e., a randomized, double blind, parallel, three-arm, placebo-controlled, in vivo study comparing the test product to the RLD and placebo (vehicle control), is consistent with the study design recommended in the guidance and a large number of subjects, 4,076, were enrolled.*
3. *Briefly, there are two main differences in the study design recommended in the PSG and the design of Study PRG-NY-14-008 conducted to support this ANDA:*
    a. *Age of study subjects: recommended 18 years and older vs. 12 years in the current study. However, 12 years and older is consistent with the labeled age recommendations of acyclovir topical cream per approved Zovirax product label.*
    b. *Primary endpoint: the PSG defines primary endpoints for subjects with vesicular and nonvesicular lesions; the current study only defines the primary endpoint for subjects with vesicular lesions. The study's definition of the primary endpoint for subjects with vesicular lesions is consistent with the PSG's definition, measured in the same units (hours from treatment initiation to healing).*

4. *The primary endpoint was calculated by subtracting the recorded time of the first application of study medication from the recorded time of the investigator-assessed healing with a designated window of ±2 days to complete the assessment.*

2.1.2.2 Generic Product Development

Controlled Correspondence – qualitative (Q1)/quantitative (Q2) formulation review
The only pre ANDA communication between Perrigo and the Office of Generic Drugs (OGD) for acyclovir cream product development was controlled correspondence #12-0482 on 05/07/2012, requesting confirmation of Q1/Q2 compliance of its proposed formulations for acyclovir cream, 5%. On 07/13/2012. This control was reviewed by DBII who confirmed the proposed formulation was Q1/Q2 the same as RLD.[9] A search in Mercado on 6/26/2018, identified 28 complete and 1 withdrawn controls submitted on 12/28/2005 to present. Prior to the posting of draft acyclovir PSG, most of the inquiries requested input on BE methods for generic drug development referencing Zovirax Cream, 5%. Post guidance posting, most inquiries pertain to formulation sameness (Q1/Q2 determination). There are no inquires for recommendations on clinical endpoint studies for acyclovir cream.

2.1.2.3 Relevant Communications with Other Generic Applicants

None

2.1.2.4 Other ANDA submissions for same or related product

Per Panorama Reporting search under ANDA by RLD, search term "contains 21478" on 11/25/2018, OGD has received six applications for generic acyclovir cream, 5% since 05/23/2013 to date, including this application (ANDA 208702 highlighted yellow). The search (b) (4) (b) (4). Table 1 below, summarizes the status and deficiencies of the received ANDAs.

Table 1. Current Status and Deficiencies in Acyclovir Cream Applications 2013 to Present

Application #	Applicant Holder	FDA Received	Sameness to RLD[$]	Studies Submitted	Deficiency[$]	Status
(b) (4)						

(b) (4)

Application #	Applicant Holder	FDA Received	Sameness to RLD[$]	Studies Submitted	Deficiency[$]	Status
208766	Amneal	12/30/2015	Q1/Q2/Q3	IVRT, IVPT	Inadequate IVRT and IVPT methods[14]	CR 03/24/2017 and 05/15/2018[15]
208702	Perrigo	01/07/2016	Q1/Q2/Q3	1. IVRT, IVPT 2. Clinical endpoint (04/05/2018)	1.Inadequate IVRT (first review cycle only) and inadequate IVPT methods. 2.Under review	1.CR 03/17/2017 2.Current
(b) (4)						

[$]Annotated deficiencies correspond to in vitro testing only. Complete list of deficiencies can be accessed through footnote with CR Letter link for each ANDA, when applicable
Reviewer Table.
Q1=qualitatively, Q2=quantitatively, Q3=physicochemical characterization
IVRT-in vitro release test; IVPT=in vitro permeation test
CR=Complete Response

Reviewer Comments:

1. *The current ANDA, 208702, is unique in that it is the only application for acyclovir cream, 5% that has conducted both in vitro studies and a clinical endpoint BE study, in vivo, to support approval of their application.*
2. *The acyclovir PSG revision in December 2016, provides detailed recommendations for the IVRT and IVPT methods; the level of detail for these methods was not present in the original draft PSG posted in December of 2015.* (b) (4) (b) (4).
3. *As noted, IVPT has not been found to be adequate in any of the applications to date, related to deficiencies in IVPT methods; Perrigo's IVRT was inadequate in the first review cycle, but was found to be adequate in the current review cycle.*

2.1.3 Other Relevant Information

For topical acyclovir drug products, a search of the Orange Book (OB) on 11/25/2018 retrieved 10 marketed prescription entries corresponding to cream (1 entry) and ointment (9 entries) dosage forms (see Table 2 below), but no generic acyclovir cream, 5%. (b) (4) (b) (4)

[14] A208766 BE Review by Juhyun Kim, PhD, uploaded in GDRP on 05/13/2018
[15] ANDA 208766 Complete Response Letter uploaded by Dat Doan on 05/15/2018
http://panorama.fda.gov/document/view?versionID=5afb1f3b01256eae9dac391d738a5c47
(b) (4)

Table 2. Orange Book currently approved applications for topical acyclovir (n=11)

Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
Acyclovir	Zovirax	N021478	Cream	Topical	5%		RLD	RS	Valeant
Acyclovir	Acyclovir	A209000	Ointment	Topical	5%	AB			Alembic
Acyclovir	Acyclovir	A204605	Ointment	Topical	5%	AB			Amneal
Acyclovir	Acyclovir	A206633	Ointment	Topical	5%	AB			Fougera
Acyclovir	Acyclovir	A205591	Ointment	Topical	5%	AB			G and W Lab
Acyclovir	Acyclovir	A205510	Ointment	Topical	5%	AB			Glenmark
Acyclovir	Acyclovir	A202459	Ointment	Topical	5%	AB			Mylan
Acyclovir	Acyclovir	A205469	Ointment	Topical	5%	AB			Taro
Acyclovir	Acyclovir	A206437	Ointment	Topical	5%	AB			Tolmar Inc
Acyclovir	Zovirax	N018604	Ointment	Topical	5%	AB	RLD	RS	Valeant

Source: Search on 11/25/2018 by this reviewer of the Orange Book
TE=Therapeutic Equivalence
RLD=Reference Listed Drug

Reviewer Comments:

1. *There are no approved generics for acyclovir 5% cream to date.*
2. *There are eight approved generic versions of Zovirax Ointment, 5%, NDA 018604. As noted, acyclovir ointment 5% and acyclovir cream 5 % are not therapeutically equivalent (TE); similarly, their clinical indications are not the same, i.e., the ointment is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients),*[19] *whereas the cream is labeled for herpes labialis in immunocompetent patients.*
3. *The approved generic acyclovir ANDAs relied on in vitro bioequivalence studies (no one conducted in vivo clinical endpoint BE study). The draft PSG for acyclovir ointment, recommended in March 2012, also describes an in vitro and an in vivo option to establish BE to Zovirax ointment, but no IVPT is requested based on formulation differences of ointment vs. cream.*

2.2 Description of Clinical Data and Sources

The applicant conducted one clinical endpoint bioequivalence study to compare the test acyclovir drug product to the RLD.

2.2.1 Source of Clinical Data

Study No.	PRG-NY-14-008
NCT #	02265913 (Form FDA 3674 submitted 04/05/2018)
Study Design	Randomized, double-blind, vehicle-controlled, parallel-group, multicenter, bioequivalence study
CRO(s)	Chiltern International (Wilmington, NC; formerly Theorem Clinical Research) provided project management, data management, clinical/medical monitoring, quality assurance (QA; consulting), biostatistical analysis, and preparation of the clinical study report (CSR)

[19] NDA 018604 Zovirax (acyclovir) ointment, 5% approved label 05/30/2001

	Sharp Clinical Services (Phoenixville, PA) provided labeling of study medication, assembling of study medication, storage and shipment of study medication, and preparation and storage of randomization schedule
Study Period	10/06/2014 through 04/27/2016
Study Centers[20]	A total of 97 sites within the United States randomized subjects in this study
Enrollment	A total of 4,076 subjects were enrolled

Reviewer's comments:

1. *Quorum Review IRB approved 97 sites in the US for participation and all centers randomized subjects.*
2. *Center 075 in New York (Principal Investigator (PI) Dr. Jody Greenfield) closed after enrolling three subjects into the study. These subjects, (b) (6) and Subject (b) (6), were transferred to Study Site 003, also in New York (PI Dr. Scott Bloom). Per Applicant's report, these subjects were excluded from the mITT and PP populations because they did not experience a recurrence of herpes labialis during the study period.*
3. *Transferring these subjects does not affect the study outcome as the subjects were not exposed to the study drugs and were appropriately excluded from analyses.*

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

ANDA Submission(s)	1) ANDA Submission 04/05/2018 (Unsolicited Major Amendment) 2) Clinical/Response to Information Request (IR) 07/19/2018 3) Clinical/Response to IR 07/24/2018 4) Clinical Response to IR 08/23/2018 5) FDA Product-Specific Guidance: Recommended December 2015; Revised December 2016
FDA Statistical Review	FDA Statistical Review by Somesh Chattopadhyay, PhD completed 09/27/2018
FDA OSIS Inspection	OSIS Bioequivalence Audit Request 04/11/2018): OSIS Establishment Inspection Report (EIR) by Mohsen Rajabi Abhari, PhD dated 11/30/2018

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Blinding	See Applicant's Study Report Section 9.4.6 Page 33 of 446
Randomization	See Applicant's Study Report Section 9.4.3 Page 32 of 446
Retention of Reserve Samples:	See Applicant's Study Protocol Version 4.0 dated 04/22/2016, Section 6.2.3 Page 30 of 219

Reviewer's comments:

1. *Test article control and accountability verification by OSIS Inspection was completed on 11/30/2018 and the outcome is adequate. See Section 2.6.1. for details.*
2. *Blinding, randomization, and retention of reserve samples procedures are acceptable. The Applicant's description of the blinding procedure is as follows:*

> The sponsor, sponsor representatives, subject, investigator, staff at the study site, study monitors, and data analysis/management personnel were blinded to treatment assignments. Study medication was blinded, labeled, and packaged according to the randomization code. Each subject's treatment unit consisted of one kit box containing

[20]ANDA 208702 GS 04/05/2018 Submission PRG-NY-14 BDE SEQ 0006 (7), Module 2.7.1. Clinical Summary pp. 6-18 of 63 \\cdsesub1\evsprod\anda208702\0006\m2\27-clin-sum\prg-ny-14-008-dbe-tables.docx

two tubes of study medication. One tube was distributed to the subject and the second remained at the site as a back-up sample to be distributed only if necessary. The blinded tear-off portion of the kit label identified the study medication in the kit. In the event of an emergency, the specific subject treatment could have been identified by removing the overlay of the blinded label, which was attached to the study medication dispensing log; however, every effort was made to maintain the blind. The investigator was instructed not to scratch off the occluding layer of the label unless absolutely necessary to provide medical treatment ... If the occluded portion of the label was removed, each involved subject(s) was to be discontinued from the study and the reason for breaking the blind was to be clearly documented in the source documentation and eCRF.

3. *No subjects were reported to have discontinued or withdrawn from the study for reasons of unblinding.*

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

☒ The study appears to have been conducted in accordance with accepted ethical standards

☒ The IRB approved the original protocol and the informed consent form prior to the start of the study

2.3.4 Evaluation of Financial Disclosure

☒Form FDA 3454 is submitted

Reviewer Comment: *The Applicant did not include financial disclosure information at the time of the clinical endpoint submission on 04/05/2018. Form FDA 3454 was submitted on 07/24/2018 in response to DCR request to submit financial disclosure information sent to Applicant on 07/11/2018.*

☒The Principal Investigator and all sub-investigators are listed

☒The Applicant had no financial arrangements with the investigators to disclose

2.4 Review of Bioequivalence

2.4.1 Detailed Review of a Clinical Endpoint Bioequivalence Study

DCR reviewed clinical endpoint study PRG-NY-14-008 to evaluate whether the proposed acyclovir cream, 5% formulation is bioequivalent to the RLD, Zovirax Cream, 5%.

Applicant's Study #	PRG-NY-14-008
Title	A Multicenter, Double-Blind, Randomized Vehicle-Controlled, Parallel-Group Study to compare Perrigo UK Finco's Acyclovir Cream, 5% with Zovirax® (Acyclovir) Cream 5%, and both active treatments to a vehicle control in treatment of recurrent herpes simplex labialis.
Study Design	This is a randomized double-blind vehicle-controlled parallel bioequivalence study.
Objectives	1.Compare the safety and efficacy profile of Perrigo's acyclovir cream 5% (test product) to Valeant's Zovirax cream 5% (reference product).

	2.Demonstrate the bioequivalence of the test product to the reference product as well as superior efficacy of the two active formulations over that of the vehicle in the treatment of herpes labialis in adults and adolescents 12 years of age and older.

2.4.1.1 Protocol Review

Protocol Version	Protocol Date(s)	IRB Approval Date(s)
Protocol Version 4.0	04/22/2016	05/11/2016
Protocol Amendment 3.0	04/22/2016	05/11/2016
Protocol Version 3.0	02/11/2015	02/24/2015
Protocol Version 2.0	09/04/2014	09/11/2014
Protocol Version 1.0	04/30/2014	06/06/2014

Reviewer's comments:

1. *According to the study report, the study enrollment period was 10/06/2014 to 04/27/2016. Amendment 3 documents enrollment of approximately 1,400* ***additional*** *subjects to increase the total subject number to approximately 4,100 subjects. The Applicant states, "The existing enrolled subjects had not returned with a herpes simplex labialis recurrence as per the projected recurrence rate hence the need to add more subjects to the study population." Amendment 3 is dated 04/22/2016, five days prior to the last enrollment date. Thus, DCR sent IR Letter (A028702N000DCR_InformationRequest (02) on 07/11/2018 to provide a list of subjects who were enrolled under Amendment 3 with exact dates of enrollment and indicate whether unblinding occurred prior to enrolling the additional subjects. If that was the case, DCR requested the Applicant to provide a separate dataset and analysis including only those subjects prior to unblinding, excluding data from the additional subjects. Additionally, DCR requested submitting amendments 1 and 2 and, explain what specific changes were made to each protocol amendment, and explain why the changes do not affect study outcome.* [21]
2. *The Applicant's IR response received on 07/24/2018 states, in verbatim:*

   On April 15, 2015, Perrigo stopped recruitment of subjects when our targeted number of 2,667 screened subjects was achieved. It was realized however by June 28, 2015 that the subject return rate (ie. (sic) outbreak events) was significantly lower than anticipated; 34% versus 58% and many of the subjects screened since October 2014 had not yet experienced an outbreak and many were further no longer responding to communications from the Investigator sites. Concerned that the study would be insufficiently powered, Perrigo decided to increase the study enrollment by 1,413 subjects to adequately power the study. An Administrative Letter, dated June 29, 2015, was sent to clinic sites on July 2, 2015 along with notification that the re-opening of recruitment was approved by Quorum IRB on July 1, 2015. Recruitment was officially re-opened on July 2, 2015. The result of the additional recruitment was that an additional 1,413 subjects
   were enrolled between July 3, 2015 and April 27, 2016… Perrigo did **NOT** unblind the study prior to the enrollment of the additional 1,413 subjects.

[21] IR 02 send 07/11/2018
http://panorama.fda.gov/document/view?versionID=5b46190e00888dd22b658e3d2b105f27

3. *The Applicant submitted a complete listing of the 1,413 subjects in question and their visit dates along with updated protocol amendments.*
4. *Based on the Applicant's submission, subjects were enrolled after IRB approval.*

2.4.1.2 Study Design

2.4.1.2.1 Study Visits and Procedures

Error! Reference source not found. Table 3 below outlines the study visits and procedures during each visit.

Table 3: Study Schedule†

Visit Number	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10,11,12 or Un-Scheduled Visit	Visit 13	End of Study/ Lesion Healing Day/ Early termination Visit
Visit Day		Day 1	Day 2	Day 3	Day 4 (End of study medication therapy)	Day 5	Day 6	Day 7	Day 8	Day 10,12,14, or Un-Scheduled Visit	Day 21	
Informed Consent/Assent	X											
Inclusion/Exclusion	X	X										
Medical History	X	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X										
Urine Pregnancy Test	X	X									X	X
Assess Application Site Reactions		X	X	X	X	X	X	X	X	X	X	X
Assess Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Assess Subject Compliance		X	X	X	X	X						
Dispense Subject Diary	X											
Collect and Review Subject Diary		X	X	X	X	X	X	X	X	X	X	X
Assess Lesion Healing		X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication and Application Instructions	X											
Schedule Next Visit		X	X	X	X	X*	X*	X*	X*	X*		
Collect Study Medication						X						

* If lesion not healed. Lesion healing day was the end of study visit, hence no more study visits required after that point.
† Table 2.3 order of procedures taken directly from protocol version 4.0, dated 22 April 2016
Source: Applicant's Submission, Module 2.7.1 (Table 8), page 24 of 63

Reviewer comments:

- *Per study protocol, subjects received instructions to apply the study medication within an hour of the start of signs/symptoms (prodrome) of a RHL recurrence, before the appearance of vesicles, and then 5 times a day for 4 days (regardless of healing status). Subjects were instructed to go to the study clinic within 24 hours of starting the medication for Visit 2 (Day 1 of treatment) and daily thereafter for 3 days [Visit 3 (Day*

2), Visit 4 (Day 3), and Visit 5 (Day 4). Subjects needed to return study medication on Day 5 (visit 6); for subjects whose lesions had healed prior to Day 5, Day 5 was still End of Study visit. Otherwise, daily follow up visits were planned for Days 6, 7, 8, and then for days 10, 12, 14, and 21 for subjects who did not heal prior to Day 5 (Visit 6).

- *The scheduled visits and overall procedures are consistent with the recommendations in the PSG for acyclovir cream clinical endpoint study.*

2.4.1.2.2 Treatment Arms

2.4.1.2.3 Treatment Arms Product Information

Product	Test	Reference	Placebo/Vehicle
Treatment ID (if applicable)	N/A	N/A	N/A
Product Name	acyclovir cream, 5%, Perrigo	Zovirax (acyclovir) cream 5%,	vehicle of acyclovir cream; Perrigo
Manufacturer	Perrigo Israel Pharmaceuticals Ltd.	Valeant Pharmaceuticals (formerly GlaxoSmithKline)	Perrigo Israel Pharmaceuticals Ltd.
Batch/Lot No.	070087	E3001 & A4001	071354
Manufacture Date	22 December 2013	N/A	21 January 2014
Expiration Date	N/A	Lot #: E3001; expiry date: May 2016 Lot #: A4001; expiry date: January 2017	N/A
Strength	5%	5%	N/A
Dosage Form	Cream	Cream	Cream
Dose Administered	Thin layer application of cream to clean, dry skin to cover only the cold sore or cover only the area of tingling (or other symptoms) before the cold sore appears. Rub the cream in until it disappears.	Thin layer application of cream to clean, dry skin to cover only the cold sore or cover only the area of tingling (or other symptoms) before the cold sore appears. Rub the cream in until it disappears.	Thin layer application of cream to clean, dry skin to cover only the cold sore or cover only the area of tingling (or other symptoms) before the cold sore appears. Rub the cream in until it disappears.
Dosing Regimen	five times a day for 4 days	five times a day for 4 days	five times a day for 4 days
Route of Administration	Topical	Topical	Topical

Source: Applicant's Submission, Module 2.7.1 (Table 7), page 23 of 63

Reviewer's comments:

- *The treatment regimen, application and dosing, was consistent with the recommendations in the PSG and the approved Zovirax drug product labeling.*
- *Subjects were randomized in a 1:1:1 ratio.*

2.4.1.2.4 Study Population Selection

Study PRG-NY-14-008 enrolled healthy immunocompetent male and nonpregnant and nonlactating female subjects, 12 years of age and older, with non-life-threatening recurrent herpes labialis (RHL) using the following criteria:

a. Subjects must have at least three recurrences of herpes simplex labialis per year for the past two years.
b. At least half of recurrences preceded by recognizable prodromal symptoms
c. At least half of prodromes followed by classical lesions.

Reviewer Comment: *While the PSG recommends studying adult subjects 18 years and older, Study PRG-NY-14-008 allowed for enrollment of subjects as young as 12 years age. However, of all subjects enrolled (4,076), only 81 subjects (1.98%) were younger than 18 years. A similar trend was observed among the subjects who applied the study drug at least once during the study (2,539); only 51 subjects (2%) where younger than 18. Thus, it is unlikely enrolling younger subjects affected the study outcome*

A positive viral culture was not required for enrollment. Exclusion criteria included any subject with a current episode of herpes labialis that was not completely healed, any subject who used any topical or systemic antiviral therapy or corticosteroids prior to treatment initiation and throughout the treatment and follow up, or any subject who required parenteral antiviral treatment for prior herpes labialis. For full inclusion/exclusion criteria list, see current submission, Module 2.7.1., pages 19-21 of 63.

Reviewer's comment:

1. *Consistent with acyclovir PSG, no virologic confirmation was required for entry into the study. However, it is possible that given that enrollment based on clinical diagnosis alone, may have diluted the HSV-infected population, which may further limit the ability to detect efficacy differences among the treatment groups.*
2. *Exclusion criteria are consistent with the recommendations in the acyclovir cream PSG and are acceptable.*

Criteria for removal from the study	☒Acceptable ☐Not Acceptable
Restrictions during the study	☒Acceptable ☐Not Acceptable Restrictions during the study include abstaining from the use of anti-inflammatory medications (including aspirin and non–steroidal anti-inflammatory drugs), systemic steroids, and analgesics during the treatment and follow-up periods of the study. See Applicant Study Report Section 9.3.5. page 30 of 446 for full restriction list.
Treatment compliance	75% to 125%

Reviewer Comments:

1. *Per study report, randomization/blinging was computer generated and the study drug was blinded, labeled, and packaged according to the random code, so that neither the subject nor the investigator could identify the treatment. Independent third party,* (b) (4) (b) (4)*, held the randomization code throughout the study. The Procedure for Breaking the Blind Section states,*

"In the event of an emergency, the specific subject treatment may be identified by removing the overlay of the blinded label, which is attached to the study medication log; however, every effort should be made to maintain the blind. The investigator must not scratch off the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency situation only and should seek prior authorization by the sponsor or designee when possible. The reason for breaking the blind must be clearly documented in the source documentation and CRF and the subject must be discontinued from the study."

2. *Overall the Applicant's definitions of treatment compliance, randomization/blinding procedures, and removal from the study are acceptable. No subjects were discontinued due to unblinding.*
3. *As recommended in the PSG for acyclovir cream, the study protocol contains a rescue clause to allow subjects who significantly worsen (e.g., significant increase in size or number of lesions beyond the patient's usual pattern, progression of lesions after the first few days of therapy, development of severe pain, or evidence of tissue necrosis) during therapy to be discontinued from the study and provided with standard therapy; these subjects were included in the PP population as treatment failures if the subject completed at least 3 days of treatment and had no other protocol violations. In Clinical/Response to Information Request (IR) submitted on 07/19/2018, Perrigo stated that only one subject, ((b) (6) was discontinued early from the study due to treatment failure after completing 3 days and was included in the PP as treatment failure.*[22]
4. *The Applicant's prohibited medications list is more restrictive than what is recommended in acyclovir draft PSG for acyclovir cream, as it includes restricting the use of any anti-inflammatory/analgesic drugs during the study and follow up periods. Upon a request for clarification on whether all subjects on anti-inflammatory drugs or analgesics during the study period were included or excluded from the PP population, the Applicant explained that that all subjects who reported use of anti-inflammatory medications (including aspirin and NSAIDS) and/or analgesics are included in the PP population,* ***UNLESS*** *they violated the protocol.*[23] *The response is acceptable as long as they didn't have any other significant protocol deviation and DCR confirmed there we no discrepancies in how subjects were included or excluded from analyses.*

2.4.1.2.5 Assessments

The following assessments were made during the study:

Table 4. Lesion Healing and Application Site Assessments

Assessments		Description	
Efficacy Measures	Lesion Stage	**Lesion Stage**	
		0	No signs
		1	Early signs – prodrome (itching, pain, tingling)
		2	Redness
		3	Small blister
		4	Ulcer

[22] GS Clinical/Response to Information Request dated 07/19/2018 \\cdsesub1\evsprod\anda208702\0007\m1\us\cover-letter-0007.pdf
[23] Ibid #19

Assessments		Description		
		5	Crust	
		6	Healed lesion (loss of crust and re-epithelialization with or without erythema)	
	Application Site Reactions	**Signs and Symptoms assessed:** Burning skin, cracked lips, desquamation, dry lips, dryness of skin, flakiness of skin, pruritus, and stinging on the skin were assessed as none, mild, moderate, and severe at Visit 2 (Day 1) and at each subsequent visit.		
		Site Reaction	**Description**	
		Dry lips	Dry lips	
		Desquamation	Scaly appearance of the skin	
		Dryness of skin	Dry skin	
		Cracked lips	Cracking of the skin on either the upper or lower lip	
		Burning skin	Unpleasant burning sensation of the skin	
		Pruritus	Itching sensation of the skin	
		Flakiness of the skin	Skin peeling	
		Stinging of the skin	Stinging sensation of the skin	
		Score	**Assessment**	**Description**
		0	None	Absent
		1	Mild	Slight, barely perceptible
		2	Moderate	Distinct presence
		3	Severe	Marked, intense
Safety Measures		Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), vital signs, and physical examination.		

Reviewer table. Source: Compiled from A208702 Study Report (lesions stages, p 35 of 446) and Study Protocol (application site assessment), Version 4, dated 04/22/2016, p 21 of 219

Reviewer Comments:

1. *The lesion stage classification and description used in the study is consistent with the clinical stages described FDA Recurring Herpes Labialis: Developing Drugs for Treatment and Prevention Guidance for Industry.*[24]
2. *Both the investigator and the subject performed lesion assessments outlined in the table. The subjects independently recorded the stage of their herpes lesion and the symptoms (i.e. pain, burning, stinging, itching, tingling, etc.,) twice a day, and recorded the time and date of complete healing (the time that the skin returned to normal or the time of cessation of symptoms, whichever occurred last).*
3. *Both efficacy and safety measures are consistent with the guidance and are acceptable*

2.4.1.2.6 Endpoints

Primary Endpoint	The primary efficacy endpoint was the time of complete healing of lesion. Complete healing (defined as loss of crust and re-epithelialization with or without erythema as assessed by the investigator, based on both clinical observation and review of the subject diary) was measured in hours from the time of first dosing.

[24] *Recurring Herpes Labialis: Developing Drugs for Treatment and Prevention Guidance for Industry.* November 2017 https://www fda.gov/downloads/Drugs/Guidances/UCM509410.pdf

Exploratory and Other Efficacy Endpoints	1)The elapsed time, in hours, between the subject-reported lesion healing date/time and the Investigator-assessed lesion healing date/time. The elapsed time is calculated as investigator date/time minus subject date/time. 2) Lesion stages

Reviewer Comments:

1. *The applicant's definition of the primary endpoint is consistent with the recommended primary endpoint, i.e., the duration of episode (DOE), in acyclovir PSG for subjects who experience a vesicular lesion. For subjects whose lesion is not vesicular in nature (aborted lesions), the draft PSG recommends DOE to be defined as the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last. However, the applicant did not provide any definition of time to complete healing in the case of non-vesicular primary lesion reportedly because there was no guidance before the study started. The applicant censored the subjects with non-vesicular lesions at time 0 (time of first dosing).*
2. *The primary endpoint was assessed through recorded data in the subject's diary. Within the diary, the subjects were requested to record the time and date of each application and the time the skin returned to normal or symptoms subsided (healing of lesion). As such, the primary endpoint, time to complete healing of lesion, was calculated by subtracting the subject's recorded time of the first application of the study drug from the subject's recorded time of healing. However, the subject needed an assessment within ±2 days of the recorded healing time by the investigator in order to confirm that healing had indeed occurred. In such case, the subject's recorded healing timeline was used in the primary endpoint variable and in the PP analysis. Otherwise, the subjects were excluded from the PP population.*
3. *According to the Applicant, the diary used in the study is not a validated assessment or tool to assess the primary endpoint. However, after reviewing the diary, we think the dairy appropriately captured all the clinical observations (pain, tenderness, tingling, itching, and discomfort) and stage of the herpetic lesion (normal lip, erythema, papule, vesicle, ulcer, crust), as recommended in the PSG.*
4. *Consistent with the PSG, no secondary endpoints were evaluated.*
5. *The Applicant added other efficacy endpoints such as the elapsed time, in hours, between the subject-reported lesion healing date/time and the investigator-assessed lesion healing date/time. These additional efficacy endpoints are exploratory in nature; FDA statistical analysis does not include analyses of these efficacy endpoints.*

2.4.1.2.7 Statistical Analysis Plan

See Applicant's Study Report[25], Section 9.7 and FDA Statistical Review[26], Section 3.4 for details of the statistical analysis plan.

Intent-to-treat (ITT)/Safety Population

[25] ANDA208702 Study Report, GS Module 5.3.1.2 submitted 04/05/2018, page 39 of 446 \\cdsesub1\evsprod\anda208702\0006\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\prg-ny-14-008\prg-ny-14-008-protocol.pdf

[26] ANDA 208702 Statistical Primary Review (A208702N000DBIII-Review) by Somesh Chattopadhyay, PhD., Completed on 09/27/2018, http://panorama.fda.gov/document/view?versionID=5bad5ae0001ce01b6b7bce152e3f3844

Subjects who were randomized, and dispensed study medication regardless of if the medication was used or not by the subject.

Modified intent-to-treat (mITT) Population

The mITT Population included all randomized subjects who met Visit 2 (Day 1 of treatment) inclusion/exclusion criteria, applied at least one dose of assigned product, and returned for at least one post-screening efficacy assessment.

Per-protocol (PP) Population

Subjects who met the following criteria

- Met Visit 2 inclusion/exclusion criteria
- Randomized, dispensed, and met the protocol criteria for treatment compliance, i.e., received at least 75% and not more than 125% of intended doses and did not miss more than five consecutive doses
- Had no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy
    - Had Visit 2 investigator assessment within +2 days of first treatment;
    - Did not take any prohibited medications;
    - Subject-reported healing and had investigator-healing assessment within +2 days of subject-reported healing time.

Subjects who did not have subject-reported healing, but met the other criteria for PP, could have been included in the PP population per the following:

- Subjects who discontinued early (or completed the study) after completing at least 3 days of treatment, did not heal, and were declared treatment failures were included in the PP population provided that there were no other protocol violations identified prior to their discontinuation. Subjects who discontinued early (or completed the study) but were not treatment failures were excluded from the PP population.
- Subjects whose primary lesions were not vesicular in nature (aborted lesions), but initiated study treatment, completed the study, and met all the above criteria were included in the PP population.
- Subjects who did not experience a prodrome, but initiated study treatment, completed the study, and met all the above criteria will be included in the PP population.

Reviewer Comments:

1. *The Applicant used the same definition for the safety and ITT populations. The definition is consistent with the generally used definition for the ITT population, but not the safety population. The subjects should have taken at least one dose of study medication to be included in the safety population and should be classified as treated, not as randomized.*
2. *The definition of the mITT and PP population are consistent with the PSG for acyclovir cream. Per PSG guidance, the PP population should comprise "all randomized subjects who meet all inclusion/exclusion criteria, applied a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than 1 consecutive day, and complete the evaluation within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation."*

3. *The guidance also recommends including subjects discontinued early due to lack of treatment effect after completing 3 days as treatment failures but does not addresses subjects with aborted lesions or without prodrome. As mentioned in Section 2.4.1.2.3, only one subject, (b) (6) was discontinued early from the study due to treatment failure after completing 3 days and was included in the PP as treatment failure.*[27]

2.4.1.3 Study Subjects

2.4.1.3.1 Subjects Analyzed

Study PRG-NY-14-008 randomized 4,076 subjects, 1,357 to the test product, 1,361 to the reference product and 1,358 to vehicle. Among them, 2,416 subjects (793 in the test arm, 810 in the reference arm and 813 in the vehicle arm) completed the study. Out of 4,076 subjects, 1,537 subjects were not dosed. These subjects were excluded from the safety population by FDA, which is consistent with the generally used definition for the safety population that subjects should have taken at least one dose of the study drug, but not by the Applicant. Thus, DCR requested the Applicant to reanalyze the data excluding subjects who were not exposed to the study drugs. The Applicant resubmitted the data excluding subjects who were not dosed (1,537 subjects) in Clinical/Response to Information Request dated 08/23/2018.[28] FDA mITT population comprised all subjects who were dosed (excluded only the 1,537 subjects who were not dosed); the Applicant excluded an additional 74 subjects from the mITT population. Determination of analysis populations by both the Applicant and FDA is presented in Table 5.

Table 5: Number of Subjects in the Applicant and FDA Safety, mITT and PP Populations

	Applicant's Determination				FDA's Determination			
	Test	**Reference**	**Vehicle**	**All**	**Test**	**Reference**	**Vehicle**	**All**
Enrolled (randomized)	1357	1361	1358	4076	1357	1361	1358	4076
Safety Population	1357 (100%)	1361 (100%)	1358 (100%)	4076 (100%)	836 (61.61%)	856 (62.69%)	847 (62.37%)	2539 (62.29%)
Excluded from safety population					521 (38.39%)	505 (37.11%)	511 (37.63%)	1537 (37.71%)
Reasons for exclusion from safety population								
Not dosed					521	505	511	1357
Modified Intent-to0treat (mITT) Population	806 (59.4%)	835 (61.35%)	824 (60.68%)	2465 (60.48%)	836 (61.61%)	856 (62.69%)	847 (62.37%)	2539 (62.29%)
Excluded from mITT population	551 (40.46%)	526 (38.65%)	534 (39.32%)	1611 (39.53%)	521 (38.39%)	505 (37.11%)	511 (37.63%)	1537 (37.71%)
Reasons for exclusion from mITT population								
Not dosed	521	505	511	1537	521	505	511	1537
Did not meet I/E criteria at Visit 2	11	7	11	29				
Missing I/E at Visit 2	13	12	9	34				
No post-screening healing assessment	3	0	2	5				

[27] GS Clinical/Response to Information Request dated 07/19/2018
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[28] GS Clinical/Response to Information Request dated 08/23/2018
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	Applicant's Determination				FDA's Determination			
	Test	**Reference**	**Vehicle**	**All**	**Test**	**Reference**	**Vehicle**	**All**
Manually removed from mITT population	3	2	1	6				
Per-Protocol (PP)Population	639 (47.09%)	662 (48.64%)	647 (47.64%)	1948 (47.79%)	639 (47.09%)	662 (48.64%)	647 (47.64%)	1948 (47.79%)
Excluded from PP population	718 (52.91%)	699 (51.36%)	711 (52.36%)	2128 (52.21%)	718 (52.91%)	699 (51.36%)	711 (52.36%)	2128 (52.21%)
Reasons for exclusion from PP population								
Not dosed	521	505	511	1537	521	505	511	1537
Did not meet I/E criteria at Visit 2	11	7	11	29	11	7	11	29
Missing I/E criteria at Visit 2	13	12	9	34	13	12	9	34
No post-screening healing assessment	3	0	2	5	3	0	2	5
Manually removed from mITT/PP population	3	2	1	6	3	2	1	6
PV per CRA log	3	5	3	11	3	5	3	11
Completed/discontinued study and did not assess lesion healing	2	2	2	6	2	2	2	6
Did not have investigator healing assessment within +2 days of subject-reported healing time	48	43	57	148	48	43	57	148
Did not have visit 2 assessment within +2 days of first treatment	27	19	27	73	27	19	27	73
Did not meet study medication compliance criteria	25	34	25	84	25	34	25	84
Subject did not report healing. Investigator assessed that healing occurred but cannot determine healing time	55	53	50	158	55	53	50	158
Missed more than 5 consecutive applications of study medication	1	2	2	5	1	2	2	5
Subject reported healing, but did not include healing date/time	5	11	8	24	5	11	8	24
Subject reported healing, but investigator did not confirm healing	1	2	1	4	1	2	1	4
Prohibited medication	0	2	2	4	0	2	2	4

Source: Applicant's Clinical Summary, GS Module 2.7.1. Table 9 (p. 25 of 63) and FDA Statistical Review, Table 2, p.16-17.

* PV = Protocol Violation; CRA = clinical research associate

Reviewer Comments:

1. *Study PRG-NY-14-008 enrolled a large number of subjects, but attrition rate was high. As noted in the table, of the 4,076 subjects randomized, 2,128 subjects were not included in the PP population; the most common reason for exclusion was "subject not dosed (1,537 subjects). The most common reasons for not dosing were not shown in the table. Other reasons for exclusion are as follows:*
    1. *Subject did not experience recurrence = 669 subjects (16.4%):*
        a. *221 in the test arm*

   b. *227 in the RLD arm*
   c. *121 in the placebo arm*
2. *Lost to follow up = 449 subjects (11%):*
   a. *149 in the test arm*
   b. *154 in the RLD arm*
   c. *147 in the placebo arm*
3. *Withdrew consent = 186 subjects (4.5%):*
   a. *62 in the test arm*
   b. *62 in the RLD arm*
   c. *59 in the placebo arm*
4. *Other = 333 (8.2%):*
   a. *120 in the test arm*
   b. *101 in the RLD arm*
   c. *112 in the placebo arm*

2. *Thus, subject distribution appears fairly balanced between the treatment groups.*

2.4.1.3.2 Demographics & Baseline Characteristics

The following table provides the demographic and baseline characteristics for the safety population.

Table 6: Summary of Demographic and Baseline Characteristics in the Safety Population

Demographic/Baseline Characteristics	Acyclovir Cream 5% (N=1357) n (%)	Zovirax Cream 5% (N=1361) n (%)	Vehicle (N=1358) n (%)	All Subjects N=4076) n (%)
Age (year)				
N	1357	1361	1358	4076
Mean (SD)	43.7 (15.05)	43.9 (15.20)	43.3 (14.99)	43.7 (15.08)
Median	44.0	44.0	44.0	44.0
Min, Max	12, 87	12, 85	12, 85	12, 87
Sex				
Male	457 (33.7)	446 (32.8)	456 (33.6)	1359 (33.3)
Female	900 (66.3)	915 (67.2)	902 (66.4)	2717 (66.7)
Ethnicity				
Hispanic or Latino	278 (20.5)	297 (21.8)	300 (22.1)	875 (21.5)
Not Hispanic or Latino	1079 (79.5)	1064 (78.2)	1057 (77.8)	3200 (78.5)
Race				
Black or African American	294 (21.7)	284 (20.9)	244 (18.0)	822 (20.2)
American Indian or Alaska	6 (0.4)	6 (0.4)	4 (0.3)	16 (0.4)
Native				
Asian	9 (0.7)	12 (0.9)	9 (0.7)	30 (0.7)
Native Hawaiian or other	3 (0.2)	3 (0.2)	3 (0.2)	9 (0.2)
Pacific Islander				
White or Caucasian	1025 (75.5)	1037 (76.2)	1078 (79.4)	3140 (77.0)
Other	20 (1.5)	19 (1.4)	20 (1.5)	59 (1.4)
Height (cm)				
N	1248	1251	1253	3752
Mean (SD)	168.08 (16.983)	168.46 (15.345)	168.05 (16.199)	168.19 (16.186)
Median	167.60	167.60	167.60	167.60

Demographic/Baseline Characteristics	Acyclovir Cream 5% (N=1357) n (%)	Zovirax Cream 5% (N=1361) n (%)	Vehicle (N=1358) n (%)	All Subjects N=4076) n (%)
Min, Max	63.0, 429.3	118.0,439.4	59.0, 444.5	59.0, 444.5
Weight (kg)				
N	1256	1259	1256	3771
Mean (SD)	82.46 (21.921)	83.01 (21.849)	81.91 (21.354)	82.46 (21.709)
Median	79.80	79.80	78.90	79.40
Min, Max	42.2, 205.0	36.3, 245.0	37.6, 186.0	36.3, 245.0
BMI (kg/m^2)				
N	1245	1251	1248	3744
Mean (SD)	29.65 (10.841)	29.42 (7.651)	29.60 (14.065)	29.56 (11.159)
Median	27.90	28.10	27.70	27.90
Min, Max	3.5, 174.9	3.8, 89.9	3.3, 388.6	3.3, 388.6

Abbreviations: BMI=body mass index; ITT=intent to treat; max=maximum; min=minimum; SD=standard deviation.
Note: Percentages are based on the number of subjects enrolled in each treatment group. BMI(kg/m2) =Weight(kg)/Height(m)2.
Source: Applicant's Study Report, GS Module 5.3.1.2. Table 11-2 (p. 57 of 447)

Reviewer comments:

1. *The baseline characteristics of the study population did not differ between the study groups, with mean age of 43.7 years. Seventy percent (77%) of the study participants were white and about 20% were blacks and other minority groups; 66% were women. In the RLD trials, about 75% of the study participants were white female patients, with less than 6% minority representation.*
2. *The submitted demographic data do not include information on baseline RHL recurrence rate of the study population. The RLD reported a median of 5 episodes of RHL in last 12 months with a median of 5 episodes producing classical lesions in the last 12 months.*

2.4.1.4 Results

The primary efficacy endpoint was the time of complete healing of lesion, defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on both clinical observation and review of the subject diary, measured in hours from the time of first dosing. There are no prespecified secondary endpoints.

2.4.1.4.1 Bioequivalence Analysis Results

The Applicant and FDA statistician's bioequivalence analysis results are provided in Table 7.

Table 7. Analysis of Primary Endpoint: Bioequivalence of acyclovir cream 5% (Test) with Zovirax Cream 5% (Reference) for Time to Healing of Lesions (hours)

Time to Healing of Lesions (hours)	Applicant		FDA	
PP Population				
	Acyclovir Cream 5% (N=639)	Zovirax Cream 5% (N=662)	Acyclovir Cream 5% (N=639)	Zovirax Cream 5% (N=662)
Mean (SD)	107.57 (80.599)	109.71 (82.807)	107.57 (80.599)	109.71 (82.807)

Time to Healing of Lesions (hours)	Applicant		FDA	
PP Population				
LS means (SE)	104.81 (3.129)	106.34 (3.065)	105.02 (3.776)	106.75 (3.635)
Ratio of LS means (Test/Reference) 90% CI for Test and RLD	0.99 [0.92, 1.06]		0.98 [0.92, 1.05]	
mITT Population				
	Acyclovir Cream 5% (N=806)	Zovirax Cream 5% (N=835)	Acyclovir Cream 5% (N=836)	Zovirax Cream 5% (N=856)
Mean (SD)	145.61 (138.636)	146.40 (140.164)	152.55 (146.128)	151.82 (146.594)
LS means (SE	141.16 (5.060)	140.16 (5.042)	147.71 (6.590)	145.63 (6.504)
Ratio of LS means (Test/Reference) 90% CI for Test and RLD	1.01 [0.93, 1.09]		1.01 [0.94, 1.10]	

Source: Reviewer's Table compiled from Applicant's Study Report, Table 11-4 (p. 58 of 446) & FDA Statistical Review, Table 8 & 10.

Reviewer Comments:

1. *Per Applicant, BE testing based on the PP population served as definitive analysis and testing based on the mITT population served as supportive analysis.*
2. *Time to healing cut off is 21 days.*
3. *According to the Applicant's and FDA statistical analysis results for the primary endpoint, the 90% CI of the difference in time to healing between the test and reference products in the PP population was within acceptable BE limits of [0.80, 1,25].*

2.4.1.4.2 Superiority Analysis Results

The Applicant and FDA statistician's superiority analysis results are provided in Table 8.

Table 8: Superiority Analysis of Time to Complete Healing of Lesions

Time to healing of esions (hours)	Applicant			FDA		
	PP Population					
	Acyclovir Cream 5%	Zovirax Cream 5%	Vehicle	Acyclovir Cream 5%	Zovirax Cream 5%	Vehicle
N	639	662	647	639	662	647
Mean (SD)	107.57 (80.599)	109.71 (82.807)	112.05 (83.343)	107.57 (80.599)	109.71 (82.807)	112.05 (83.343)
Comparison with vehicle						
Difference in LS means (SE)	-5.28 (4.068)	-3.38 (4.021)		-5.43 (4.093)	-3.73 (4.035)	
95% CI	[-13.26, 2.70]	[-11.27, 4.50]		[-13.46, 2.60]	[-11.64, 4.19]	
p-value	0.1946	0.4000		0.1849	0.3559	
	MITT Population					

Time to healing of esions (hours)	Applicant			FDA		
	PP Population					
	Acyclovir Cream 5%	Zovirax Cream 5%	Vehicle	Acyclovir Cream 5%	Zovirax Cream 5%	Vehicle
	Acyclovir Cream 5%	Zovirax Cream 5%	Vehicle	Acyclovir Cream 5%	Zovirax Cream 5%	Vehicle
N	806	835	824	836	856	847
Mean (SD)	145.61 (138.636)	146.40 (140.164)	147.28 (136.909)	152.55 (146.128)	151.82 (146.594)	150.78 (140.619)
Comparison with vehicle						
Difference in LS means (SE)	-1.40 (6.494)	-2.53 (6.434)		1.14 (6.709)	0.11 (6.702)	
95% CI	[-14.14, 11.33]	[-15.14, 10.09]		[-12.02,14.30]	[-13.03,13.26]	
p-value	0.8288	0.6945		0.8646	0.9864	

Source: Reviewer's Table compiled from Applicant's Study Report, Table 11-5 (p. 59 of 446) & FDA Statistical Review, Table 9 & 12.

Reviewer comment:

1. *Time to complete healing (mITT population) in this study was much longer than the healing time in the clinical trials of RLD, even for the subjects in the RLD arm. Specifically, mean times to heal in one of the RLD trials were 4.74 days for Zovirax and 5.2 days for the placebo arm whereas in this study mean healing times were 6.4 days (152.55 h/24h) in the test arm and 6.3 days (151.82/24 h) in the RLD arm.*
2. *As noted, both the test and RLD products demonstrated no superiority to placebo, which indicates the study lacks sensitivity to detect any difference between the treatment groups and cannot support bioequivalence between the test and reference products. However, the lack of superiority against placebo for both the RLD and the test product may be related to the fact that vehicle itself may have some treatment effect.*
3. *Based on the natural history of RHL, the mean (± SD) time from onset of the first physical sign to complete healing is 200±102 hours, i.e., 8±4 days.[29] The possible treatment effect of the vehicle was also observed in Medical and Biometrics Review of the Zovirax Cream (NDA 021478) dated 12/20/2012, which states,[30]*

   "The vehicle may be exerting some clinical benefit because the mean time to healing for participants using the vehicle control was approximately five days, much shorter than time to healing reported in historical observational studies without treatment."

[29] Spotswood Spruance et al., (1977) The Natural History of Recurrent Herpes Simplex Labialis. N Engl J Med 297:69-79

[30] NDA 021478 Zovirax Cream, 5% Medical and Biometrics Review of the Zovirax Cream by Joseph G Toerner, dated 12/20/2012

2.4.1.4.3 Subset Analyses

A total of 358 subjects (112 in the test arm, 126 in the reference arm, and 120 in the vehicle arm) had nonvesicular lesions, which the Applicant classified as "aborted lesion". The applicant's definition of aborted lesion is, "a typical, recurrence-associated localized, site-specific prodrome and/or redness and/or papule, which completely resolves without ever progressing to the vesicular stage." In Clinical/Response to Information Request dated 08/23/2018, the Applicant states,

> "… subject's [sic]were considered to have experienced an aborted lesion if the Subject diary denotes "Lesion Never Developed" or investigator assessment denotes "N/A Lesion has not developed". These subjects were to be assigned a value of zero (0) for time-to-complete healing of lesions. This was determined appropriate since a value of time to healing for this study was defined by the recorded time of "crust spontaneously falling off" and since aborted episodes never resulted in a vesicular
> lesion/blister, there would be no appropriate synonymous healing time to report for such subjects.
>
> Because subjective prodromal signs/symptoms are independent subject-based self-assessments, cultures cannot be collected on non-vesicular targets, and signs/ symptoms of suggested prodromes could not be confirmed. In addition, both product-specific Bioequivalence FDA guidances for Acyclovir Cream and Ointment do not require a positive viral culture for enrollment."

Because it cannot be objectively confirmed whether these subjects indeed had an HSV recurrence, DCR was concerned that they may "dilute" the study population making it more difficult to detect any differences between the treatment groups if there was a difference. DCR was also concerned that since these subjects were assigned a value of zero for the primary endpoint, time to complete healing, the average time to complete healing may appear smaller than they actually are. To address this issue, DCR requested the statistician reviewer perform equivalence analyses in both FDA's PP and mITT populations excluding the subjects who had an aborted lesion. Table 9 summarizes FDA's equivalence analyses of time to complete healing in FDA's PP and mITT Populations excluding subjects with aborted lesions.

Table 9. Equivalence Analyses of Time to Complete Healing in FDA's PP and mITT Populations Excluding Subject with Aborted Lesions

	Test	Reference
Per-Protocol (PP) Population		
Number of Subjects Mean (SD) LS means (SE)	534 128.72 (71.050) 123.92 (3.141)	553 131.34 (73.251) 127.43 (3.045)
Ratio of LS means (Test/Reference) 90% confidence interval	0.97 (0.93,1.02)	
Modified Intent-to-Treat (mITT) Population		
Number of Subjects Mean (SD) LS means (SE)	724 176.15 (143.173) 169.30 (6.433)	730 178.02 (143.292) 168.92 (6.423)
Ratio of LS means (Test/Reference) 90% confidence interval	1.00 (0.94, 1.07)	

Source: FDA Statistical Review, Table 11

Reviewer Comment: *The overall results of the equivalence analyses of time to complete healing in FDA's PP and mITT Populations are the same with or without the subjects with aborted lesions.*

The analysis of superiority excluding the subjects who experienced an aborted lesion are presented in Table 10.

Table 10. Superiority Analysis of Time to Complete Healing in FDA's PP and mITT Populations Excluding Subject with Aborted Lesions

	Test	Reference	Vehicle
Modified Intent-to-Treat (mITT) Population			
Number of Subjects Mean (SD)	724 176.15 (143.173)	730 178.02 (143.292)	727 175.66 (136.617)
Comparison with Vehicle Difference in LS means (SE) 95% confidence interval P-value (two-sided)	-1.31 (6.775) (-14.60,11.98) 0.8468	-0.01 (6.887) (-13.52,13.51) 0.9993	
Per-Protocol (PP) Population			
Number of Subjects Mean (SD)	534 128.72 (71.050)	553 131.34 (73.251)	536 135.25 (72.409)
Comparison with Vehicle Difference in LS means 95% confidence interval P-value (two-sided)	-7.48 (3.555) (-14.45, -0.50) 0.0358	-5.17 (3.471) (-11.98,1.64) 0.1356	

Source: FDA Statistical Review, Table 13

Reviewer Comment:
As shown in the table, only in the PP population excluding the subjects with aborted lesions was any group (in this case, the Test group) able to show statistically significant superiority over vehicle (p-value: 0.0358). All other comparisons failed to show statistically significant superiority of test or reference over vehicle.

2.5 Comparative Review of Safety

2.5.1 Description of Adverse Events

The Applicant's safety population originally comprised all subjects that were enrolled, i.e., 4,076 subjects, which is not consistent with the generally used definition for the safety population that subjects should take at least one dose of the study drug to be included in the safety population. DCR requested the Applicant to reanalyze and resubmit the data excluding subjects who were not exposed to the study drugs. The Applicant resubmitted the data on 08/23/2018 (Clinical/Response to Information Request dated 08/23/2018).[31] The study population now

[31] GS Clinical/Response to Information Request dated 08/23/2018
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comprises 2,539 subjects who applied the study drug: 836 subjects (test), 856 subjects (RLD), and 847 (placebo) and the 1,537 subjects who were not dosed were excluded.

A total of 141 subjects [44 (5.3%) subjects in the test arm, 61 (7.1%) in the RLD, and 36 (4.3) in the placebo arm] reported 169 adverse events (AE); most AEs were mild (85 subjects) or moderate (50 subjects) in nature. Two subjects (0.2%) in the test arm and 4 subjects (0.5%) in the reference arm experienced treatment-emergent SAEs. These SAEs were atrial fibrillation and thyroid cancer in the test group and forearm fracture, dehydration, nephrolithiasis, and hypertension in the reference product group. Another subject in the test arm reported cancer (non–treatment-emergent). None of these SAEs were considered related to study drugs. There were no deaths in this study.

Six subjects interrupted or discontinued the study due to AEs: 4 (0.5%) subjects in the test arm and 2 (0.2%) subjects in the reference for reasons likely unrelated to the study drugs. The AEs per treatment arm were:

- Test: Dizziness, hypoesthesia, atrial fibrillation, palpitations, and viral infection.
- Reference: Paresthesia, facial edema, and pruritus.

The most frequent AEs were infectious, nervous system, or gastrointestinal (GI) in nature:

- Infectious AEs: upper respiratory tract infection (URI), nasopharyngitis, sinusitis, cellulitis, conjunctivitis, cystitis, gastrointestinal (viral), viral infection, influenza, and localized infection:
    - 9 subjects (1.1%), test
    - 10 subjects (1.2%), RLD
    - 12 subjects (1.4%), placebo
- Nervous system disorders: headache, dizziness, hypoesthesia, paresthesia, sinus headache, migraine, nerve compression, sciatica:
    - 13 subjects (1.6%), test
    - 8 subjects (0.9%), RLD
    - 8 subjects (0.9%), placebo
- Gastrointestinal disorders: diarrhea, dry mouth, nausea, gingival pain, abdominal pain/distention, discomfort/pain, aphthous ulcers, constipation, dyspepsia, enteritis, GI reflux, hematochezia, lip swelling, lip ulceration, oral discomfort
    - 7 subjects (0.8%), test
    - 12 subjects (1.4%), RLD
    - 8 subjects (0.9%), placebo

Application site reactions (burning, cracked lips, desquamation, dry lips, dryness of skin, flakiness of skin, pruritus, and stinging of the skin) were assessed at each visit as part of the herpes lesion assessment and were considered AE only if they warranted temporary discontinuation of the study drug. As AE, each application site reaction occurred in less than 1% per treatment arm consistent with application site reactions observed in the RLD. Per RLD labeling, acyclovir has irritation and contact sensitization potential. This was not evaluated in the study, but based on the formulation sameness between products, there is low expectation that there would be a difference in irritation and contact sensitization potentials between products. In addition, no subject reported difference in AEs in this study to warrant further evaluation of irritation and sensitization.

The following tables provide a summary of AEs (Table 11) and comparison of application site reactions between the treatment groups (Table 12).

Table 11: Summary of Adverse Events in the Safety Population

Description	Test n (%)	RLD n (%)	Vehicle n (%)	Total (subjects)
Subjects in Safety Population	836 (61.6)	856 (62.9)	847 (62.4)	2,539
Number of subjects who had an AEs (%)*	44 (5.3)	61 (7.1)	36 (4.3)	141
Number of AEs reported	51	75	43	169
Number of subjects who had a non-treatment-related AE*	1	0	0	1
Subjects with at least one related[b] event	6 (0.7)	10 (1.2)	4 (0.5)	20
Infections and infestations	1 (0.1)	0	0	1
Cellulitis	1 (0.1)	0	0	1
Nervous system disorders	2 (0.2)	2 (0.2)	0	4
Dizziness	1 (0.1)	0	0	1
Hypoaesthesia	1 (0.1)	1 (0.1)	0	2
Paraesthesia	0	1 (0.1)	0	1
Gastrointestinal disorders	2 (0.2)	1 (0.1)	2 (0.2)	5
Dry mouth	2 (0.2)	1 (0.1)	0	3
Nausea	0	0	1 (0.1)	1
Respiratory, thoracic, and mediastinal disorders	0	1 (0.1)	0	1
Dyspnoea				
Injury, poisoning, and procedural complications	0	1 (0.1)	0	1
Accidental exposure to product	0	0	1 (0.1)	1
General disorders and administration site conditions				
Pain	0	0	1 (0.1)	1
Application site reaction	0	3 (0.4)	2 (0.2)	5
Application site swelling	0	1 (0.1)	0	1
Face oedema	0	1 (0.1)	0	1
Localised oedema	0	0	1 (0.1)	1
Skin and cutaneous tissue disorders	0	4 (0.5)	0	4
Rash	0	2 (0.2)	0	2
Pruritus	0	1 (0.1)	0	1
Dermatitis contact	0	1 (0.1)	0	1
Rash generalized	0	1 (0.1)	0	1
Reproductive system and breast disorders	1 (0.1)	0	0	1
Dysmenorrhea	1 (0.1)	0	0	1
Cardiac disorders	1 (0.1)	0	0	1
Palpitations	1 (0.1)	0	0	1
Severity of AEs				
Mild	28 (3.3)	35 (4.1)	22 (2.6)	85
Moderate	14 (1.7)	22 (2.6)	14 (1.7)	50
Severe	2 (0.2)	4 (0.5)	0	6
Most frequently reported AEs*				
Infection[a]	9 (1.1)	10 (1.2)	12 (1.4)	31
Headache	9 (1.1)	3 (0.4)	6 (0.7)	18
Oropharyngeal Pain	2 (0.2)	4 (0.5)	0	6
Dry mouth	2 (0.2)	1 (0.1)	0	3
SAE (%)*	2 (0.2)	4 (0.5)	0 (0.0)	6
Death	0	0	0	0
Number of subjects discontinued study drug due to AE (%)*	4 (0.5)	2 (0.2)	0 (0.0)	6

Description	Test n (%)	RLD n (%)	Vehicle n (%)	Total (subjects)
Number of AEs leading to discontinuation of the study	5	3	0	8

Source: Applicant's Study Report, Sections 12.2-12.5 (p. 66 of 446) and Tables 12-1 thru 12-5 and "adae.xpt" dataset[32].

*Percentages are based on the number of subjects in the Safety population. Subjects are counted once within each AE. ** Applicant's Study Report; Table 12-3. [a] Includes upper respiratory tract infection (URI), sinusitis, cellulitis, conjunctivitis, cystitis, gastrointestinal (viral), viral infection, influenza, nasopharyngitis.

Reviewer Comments:

1. *Overall, the frequency of AEs in this study is very low as is expected in patients with recurrence of herpes labialis; most AEs that may be attributed to therapy are also mild.*
2. *The number of patients with at least one AE is comparable (test 6 [0.7%]; RLD 10 [1.2%], and placebo 4 [0.5%]). The number of AEs reported is higher in the reference group (61 subjects vs. 44 in the test arm and 36 in the placebo arm), but this may be due to chance. The study did not raise any new safety signal.*
3. *There were no deaths in this study. Serious AE were reported for three subjects in the test arm (atrial fibrillation, colon cancer, and thyroid cancer) and four patients in the RLD arm (forearm fracture, dehydration, nephrolithiasis, and hypertension. These SAEs were not considered treatment related.*
4. *Application site reactions (burning, cracked lips, desquamation, dry lips, dryness of skin, flakiness of skin, pruritus, and stinging of the skin) were assessed at each visit as part of the herpes lesion assessment and were considered AE only if they warranted temporary discontinuation of the study drug. As AE, each application site reaction occurred in less than 1% per treatment arm consistent with application site reactions observed in the RLD.*

Table 12 shows representative application site reaction data from Visit 2 (Day 1) and Visit 6 (Day 5). For full per visit details, refer to Clinical Study Report, Tables 14.3.4.1, pages 417 thru 440 of 446.

Table 12: Application Site Reaction by Visit Safety Population

Visit 2 (Day 1)				Visit 5 (Day 4)			
Application Site Reaction	**Test *N=1357 N (%)**	**RLD N=1361 N (%)**	**Vehicle N=1358 N (%)**	**Application Site Reaction**	**Test N=1357 N (%)**	**RLD N=1361 N (%)**	**Vehicle N=1358 N (%)**
**n	796	822	809	n	739	748	752
Burning Skin				Burning Skin			
None	445 (32.8)	450 (33.1)	452 (33.3)	None	571 (42.1))	568 (41.7)	591 (43.5)
Mild	244 (18.0)	252 (18.5)	260 (19.1)	Mild	128 (9.4)	121 (8.9)	98 (7.2)
Moderate	92 (6.8)	102 (7.5)	80 (5.9)	Moderate	33 (2.5)	46 (3.4)	56 (4.1)
Severe	15 (1.1)	18 (1.3)	17 (1.3)	Severe	6 (0.4)	13 (1.0)	7 (0.5)
Cracked Lips				Cracked Lips			
None	694 (51.1)	718 (52.8)	711 (52.4)	None	616 (45.4)	617 (45.3)	637 (46.9)
Mild	72 (5.3)	77 (5.7)	78 (5.7)	Mild	98 (7.2)	92 (6.8)	86 (6.3)
Moderate	24 (1.8)	23 (1.7)	17 (1.3)	Moderate	24 (1.8)	31 (2.3)	29 (6.3)
Severe	6 (0.4)	4 (0.3)	3 (0.2)	Severe	1 (0.1)	8 (0.6)	0

[32] \\cdsesub1\evsprod\anda208702\0006\m5\datasets\prg-ny-14-008\analysis\adam\datasets\adae.xpt

Visit 2 (Day 1)				Visit 5 (Day 4)			
Application Site Reaction	**Test *N=1357 N (%)**	**RLD N=1361 N (%)**	**Vehicle N=1358 N (%)**	**Application Site Reaction**	**Test N=1357 N (%)**	**RLD N=1361 N (%)**	**Vehicle N=1358 N (%)**
n	796	822	809	**n**	739	748	752
Desquamation				Desquamation			
None	699 (51.5)	736 (54.1)	715 (52.7)	None	617 (45.5)	655 (48.1)	631 (46.5)
Mild	72 (5.3)	65 (4.8)	74 (5.4)	Mild	95 (7.0)	66 (4.8)	95 (7.0)
Moderate	24 (1.8)	19 (1.4)	16 (1.2)	Moderate	23 (1.7)	23 (1.7)	24 (1.8)
Severe	1 (0.1)	2 (0.1)	4 (0.3)	Severe	4 (0.3)	4 (0.3)	2 (0.1)
Dry Lips				Dry Lips			
None	490 (36.1)	476 (35.0)	467 (34.4)	None	426 (31.4)	448 (32.9)	426 (31.4)
Mild	203 (15.0)	235 (17.3)	237 (17.5)	Mild	233 (17.2)	209 (15.4)	245 (18.0)
Moderate	95 (7.0)	102 (7.5)	95 (7.0)	Moderate	69 (5.1)	73 (5.4)	75 (5.5)
Severe	8 (0.6)	9 (0.7)	10 (0.7)	Severe	11 (0.8)	18 (1.3)	6 (0.4)
Dryness of Skin				Dryness of Skin			
None	627 (46.2)	641 (47.1)	611 (45.0)	None	528 (38.9)	567 (41.7)	551 (40.6)
Mild	112 (8.3)	140 (10.3)	153 (11.3)	Mild	168 (12.4)	136 (10.0)	152 (11.2)
Moderate	53 (3.9)	38 2.8)	35 (2.6)	Moderate	34 (2.5)	33 (2.4)	43 (3.2)
Severe	4 (0.3)	3 (0.2)	10 (0.7)	Severe	9 (0.7)	12 (0.9)	6 (0.4)
Flakiness of Skin				Flakiness of Skin			
None	736 (54.2)	758 (55.7)	738 (54.3)	None	631 (46.5)	640 (47.0)	621 (45.7)
Mild	46 (3.4)	55 (4.0)	57 (4.2)	Mild	85 (6.3)	89 (6.5)	105 (7.7)
Moderate	13 (1.0)	8 (0.6)	12 (0.9)	Moderate	18 (1.3)	17 (1.2)	22 (1.6)
Severe	1 (0.1)	1 (0.1)	12(0.1)	Severe	5 (0.4)	2 (0.1)	4 (0.3)
Pruritus				Pruritus			
None	456 (33.6)	496 (36.4)	481 (35.4)	None	557 (41.0)	555 (40.8)	572 (42.1)
Mild	230 (16.9)	213 (15.7)	216 (15.9)	Mild	150 (11.1)	144 (10.6)	131 (9.6)
Moderate	90 (6.6)	86 (6.3)	83 (6.1)	Moderate	28 (2.1)	37 (2.7)	42 (3.1)
Severe	20 (1.5)	27 (2.0)	29 (2.1)	Severe	4 (0.3)	12 (0.9)	7 (0.5)
Stinging				Stinging			
None	464 (34.2)	452 (33.2)	460 (33.9)	None	573 (42.2)	575 (42.2)	576 (42.4)
Mild	230 (16.9)	261 (19.2)	250 (18.4)	Mild	122 (9.0)	120 (8.8)	106 (7.8)
Moderate	90 (6.6)	91 (6.7)	82 (6.0)	Moderate	37 (2.7)	43 (3.2)	62 (4.6)
Severe	12 (0.9)	18 (1.3)	17 (1.3)	Severe	7 (0.5)	10 (0.7)	8 (0.6)

Reviewer table. Source: ANDA 208702 – AMEND-6 Clinical Study Report, Tables 14.3.4.1, pages 417 thru 445 of 446

Note: Percentages are based on the number of subjects enrolled in each treatment group (per Applicant)

*N = numbers of subjects enrolled in each treatment group

**n = number of subjects dosed and assessed

Reviewer Comment: *Overall, baseline application site reactions (Visit 2 assessment) and end of treatment assessment (Visit 5) are comparable between the groups.*

Overall, Study PRG-NY-14-008 showed no concerning clinical differences in the safety profile

between the RLD and the proposed test formulation; the frequency and nature of AEs are comparable among the treatment groups. The SAEs reported and the AEs leading to study drug interruption or discontinuation were unlikely related to the study drugs.

2.6 Relevant Findings from Other Consultant Reviews

2.6.1 Office of Study Integrity and Surveillance

Office of Study Integrity and Surveillance (OSIS)	OSIS selected the following three study sites: • Rochester Clinical Research, Inc, Rochester, NY • New River Valley Research Institute, Christiansburg, VA • Evanston Premier Healthcare Research, LLC, Evanston, IL.

The OSIS inspection report, dated 11/30/2018, concluded that no objectionable conditions were observed, and Form FDA 483 was not issued at the close-out of any of the inspections. A few items were discussed at the inspection close-outs, but the final inspection classification for all inspected sites is No Action Indicated (NAI). The inspection summary report states, in verbatim,[33]

> After reviewing the inspectional findings, I conclude the data from the audited study PRG-NY-14-008 are reliable. Thus, I recommend that the data from Study PRG-NY-14-008 be accepted for further Agency review. In addition, the data from other studies of similar design conducted at Rochester Clinical Research, Inc, Rochester, NY; New River Valley Research Institute, Christiansburg, VA; and Evanston Premier Healthcare Research, LLC, Evanston, IL before the end of the current surveillance interval should be accepted for review without an inspection.

***Reviewer's Comments**: As recommended by the OSIS, DCR concludes that the study data are acceptable for the review.*

2.6.2 Office of Biostatistics

See FDA Statistical Review by Somesh Chattopadhyay, PhD., dated 09/27/2018.[34]

***Reviewer comments**:*

1. *According to FDA statistical analyses, Study PRG-NY-14-008 showed equivalence between the test product and the RLD product for the primary endpoint but failed to showed superiority over placebo for either the RLD or the propose product. Therefore, the statisticians concluded that the study lacked sensitivity to detect true difference in clinical performance and the bioequivalence results cannot be interpreted. DCR believes that potential critical differences in the study population, i.e., severity of the recurrence and a possibly diluted herpes population, in addition to known treatment effect of the vehicle on herpes lesions, may have made it impossible for the study to pass superiority, particularly considering the modest treatment effect observed in the RLD trials of*

[33] OSIS EIR uploaded 12/03/2018 by Nicola Fenty-Stewart
http://panorama.fda.gov/document/view?versionID=5c0526940014d7b9f971f54d913afb8a
[34] ANDA 208702 Statistical Primary Review (A208702N000DBIII-Review) by Somesh Chattopadhyay, PhD., Completed on 09/27/2018,
http://panorama.fda.gov/document/view?versionID=5bad5ae0001ce01b6b7bce152e3f3844

acyclovir cream. Although the demonstration of bioequivalence between the test and RLD product is inadequate from a statistical standpoint, DCR has no clinical concerns the proposed acyclovir cream would not be therapeutically equivalent to Zovirax cream because the study showed comparative clinical response and did not raise any clinical concern from a safety perspective.

2. *The Office of Biostatistics results are provided in Section 2.4.1.4 of this review.*

2.7 Formulation

2.7.1 RLD Formulation

The formulation of the RLD, Zovirax® (acyclovir) Cream, 5%, NDA 021478 is shown below per Chemistry Review, DARRTS on 01/21/2003.[35]

Ingredient	Quantity % w/w	mg/g	Quantity/Batch
Acyclovir, USP	5.0	50	(b) (4)
Propylene Glycol, USP	(b) (4)		
White Petrolatum, USP			
Cetostearyl Alcohol, NF			
Mineral Oil, USP			
Poloxamer 407, NF			
Sodium Lauryl Sulfate, NF			
Purified Water, USP	to 100	to 1000	

2.7.2 Generic and Vehicle Control (Placebo) Formulations

Generic Formulation Acyclovir Cream, 5%

The proposed generic formulation for acyclovir cream, 5% is shown below per Section 3.2.P.1 under ANDA 208702 Major Amendment (AMEND-6) submission dated 04/05/2018.

Table 13: Generic Formulation Acyclovir Cream, 5%

Ingredient	Function	Quality Standard	Quantity		
			g/5g tube	% (w/w)	ANDA commercial batch (100 Kg) Kg
ACTIVE:					
Acyclovir	Active Ingredient	USP	0.25	5*	5*
INACTIVE INGREDIENTS:					
White Petrolatum USP	(b) (4)	USP	(b) (4)		
Cetostearyl Alcohol, NF		NF			
Mineral Oil, USP		USP			
Propylene Glycol, USP		USP			
Sodium Lauryl Sulfate, NF		NF			

[35] NDA 021478 REV-QUALITY -03 (General Review) by Zi Qiang Gu entered in DARRTS 01/21/2003

Ingredient	Function	Quality Standard	Quantity		
			g/5g tube	% (w/w)	ANDA commercial batch (100 Kg) Kg
Poloxamer 407, NF	(b) (4)	NF			(b) (4)
Purified Water (USP, EP)		USP			
TOTAL			**5g**	**100%**	**100Kg**

*Theoretical value. The actual amount is calculated according to the potency and the amount of water.

Generic Placebo Formulation, Acyclovir Cream, 5%

The placebo formulation for acyclovir cream, 5% is shown below per Clinical/Response to Information Request submitted on 07/19/2018.

Table 14. Generic Placebo Formulation, Acyclovir Cream, 5%

Ingredient	Function	Test (% w/w)	Placebo	Justification
Acyclovir	Active	5.00	-	Not included
White Petrolatum, USP	(b) (4)			(b) (4)
Cetostearyl Alcohol, NF				
Mineral Oil, USP				
Propylene Glycol, USP				
Sodium Lauryl Sulfate, NF				
Poloxamer 407, NF				
Purified Water (USP, EP)		QS to 100	QS to 100	(b) (4)

Reviewer comments:

1. *The proposed generic acyclovir cream formulation contains the same excipients at the same levels as the RLD. Thus, the proposed formulation is qualitatively (Q1) and quantitatively (Q2) the same as the RLD.*
2. *The proposed placebo formulation was received on 08/23/2018 in response to A208702N000 DCR_InformationRequest 01. There are no differences in inactive ingredients; the 5% of acyclovir was replaced with additional purified water.*
3. *There are no clinical concerns for the proposed formulations.*

2.8 Conclusion and Recommendation

2.8.1 Conclusion

Despite insufficient assay sensitivity to definitively demonstrate BE on its own, the overall results of Study PRG-NY-14-008, including comparable clinical response between the test and the reference product and no safety concerns, are adequate to provide the biorelevant information

ordinarily provided by the in vitro permeation data (IVPT). Thus, Study PRG-NY-14-008 can support the available acceptable data for the in vitro BE approach for the proposed formulation, which is Q1/Q2/Q3 the same to the RLD with acceptable in vitro release testing (IVRT) data. Therefore, based on the totality of information in the application, DCR concludes the proposed generic would likely be therapeutically equivalent to and substitutable for the RLD.

2.8.2 Recommendations

The Division of Clinical Review (DCR) recommends approval of ANDA 208702, contingent on approval recommendations from all other disciplines on the review team.

3. CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT BY THE RPM

The Clinical Discipline has completed its review and has no comments at this time.

Raquel Tapia

Digitally signed by Raquel Tapia
Date: 1/24/2019 11:17:36AM
GUID: 55a00366003903c6dd8571d1bda7d06e

Carol Kim

Digitally signed by Carol Kim
Date: 1/24/2019 11:24:34AM
GUID: 508da70a00028df5288765ab0807f9a5

Sarah Yim

Digitally signed by Sarah Yim
Date: 1/24/2019 12:34:01PM
GUID: 50841a8900009e1fe2b0e31699e4e531

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208702

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

RPM: Gwen Murphy Team Leader: Kevin Denny

☒ **PI** ☐ **PII** ☐ **PIII** ☐ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☒ **No)** ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 208702 Applicant: Perrigo UK FINCO Limited Partnership
Established Product Name: Acyclovir Cream, 5%

Basis of Submission (RLD): N021478 Zovirax Cream, 5%
Basis Of Submission Discontinued? Yes ☐ No ☒
If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?
Yes ☐ FR Notice dated _____; Document Citation _____; FR. _____(Example: 78 FR 67365)
No ☐ Consult completed but not yet published in FR

(Is ANDA based on an approved Suitability Petition? ☐ Yes ☒ No, if yes, use SP language in template)

Does the ANDA contain REMS? ☐ Yes ☒ No *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 1/28/2019**

☒ Date (Received) Acceptable for Filing -- Date **1/7/2016**
☒ Date last Complete Response (CR) letter was issued -- Date **3/17/2017**
☐ Previously reviewed and tentatively approved (if applicable) --- Date _____

YES	NO		
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Bioequivalence **1/31/2019** • Date of BE Guidance (if any) **12/2016** Date of Acceptable Labeling **9/23/2016** • Date of last RLD labeling update **4/1/2014** Date of Acceptable Quality **1/31/2019** • DMF No(s). **16144** Date(s) Acceptable **3/14/2018** • No outstanding DMF review amendments ☒ • Date of Acceptable Overall Manufacturing Inspection **1/24/2019**	If applicable: Date of Acceptable Microbiology **N/A** Date of Acceptable Clinical Review **1/24/2019** Date of Acceptable Dissolution **N/A** Date of Acceptable REMS **N/A**
☒	☐	**MMA:** All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d).	
☐	☒	Are consults pending for any discipline?	
☒	☐	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable	
☐	☒	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? If YES → OGD Policy Lead confirmed ANDA may proceed ☐; Memo uploaded (if applicable) ☐	
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews ☐	
☐	☒	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed _____	

Review Discipline/Division and RPM TL Endorsements

☒	☐	Applicable review discipline/division endorsements completed
☒	☐	RPM Team Leader endorsement completed

Additional Notes (if applicable)

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 2/1/2019
Name: IM

Patent/Exclusivity Certification:

☒ **PI** ☐ **PII** ☐ **PIII** ☐ **PIV** ☐ **section viii**

If Paragraph IV Certification- did applicant:

- Notify patent holder/NDA holder: Yes ☐ No ☐
- Was applicant sued w/in 45 days: Yes ☐ No ☐
- Has case been settled: Yes ☐ No ☐
- Applicant addressed all listed exclusivities Yes ☐ No ☐

Do the patent and exclusivity certifications align? Yes ☐ No ☐

Have there been any revisions to the use code since the original submission? Yes ☐ No ☐

RLD = **Zovirax Cream** NDA# **21478** ☒ **RX or** ☐ **OTC**

Date Checked in Orange Book#: **2/1/2019**

Type of Letter:

☒ APPROVAL

☐ TENTATIVE APPROVAL

☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)

LETTER RECOMMENDED FOR DRUGS@FDA Yes ☒ No ☐

Forfeiture Information

Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐

If yes, the date forfeiture memo was completed

Date _____ ANDA # _____

180 Day Exclusivity Information

Is applicant eligible for 180 day exclusivity Yes ☐ No ☒

- ☐ Sole
- ☐ Shared

ANDA Exclusivity for each strength: Yes ☐ No ☐

Which strength(s) eligible _____

Comments:

BOS = Zovirax Cream (NDA 21478) Application submission 1/7/2016 with a no relevant patents statement. Acknowledgment letter signed 3/3/2016.

There remains no unexpired patents or exclusivities listed in the OB to the NDA. There is no pending CP for the drug product.

Perrigo's ANDA is eligible for Full Approval. This is the first generic for the drug product.

180 Day Exclusivity Status/Landscape: N/A
Citizen Petitions Impact: N/A
First Legally Approvable Date: upon the completion of the full technical review
If Tentative Approval, anticipated full approval date: N/A

2. Final Decision

Date: 2/4/2019
Name: sgk

ANDA received on **1/7/2016** for the **5%** strength
RTR'd? Yes ☐ No ☒ If yes, RTR'd on Enter date
Priority Status? Yes ☒ No ☐ If yes, prioritization factor is **first generic**
Basis of Submission (RLD)

Drug Name	**Zovirax Cream**
NDA #	**021478**
Applicant Name	**Valeant International Bermuda**

☒ Verified the following:

1. Completion of the following endorsement tasks, if applicable:
   a. Division of Legal and Regulatory Support Endorsement
   b. Paragraph IV Evaluation
   c. REMS Endorsement
   d. Quality Endorsement
   e. Bioequivalence Endorsement
   f. Clinical-Bioequivalence Endorsement
   g. Labeling Endorsement
   h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates at Drugs@FDA since the Labeling Endorsement
5. No issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments since Quality Endorsement
9. No amendments received since the RPM Team Leader Endorsement

This ANDA is ready for **FULL** APPROVAL.

****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL****

(b) (4)

[redacted]

(b) (4)

[redacted]

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02	10/03/2017	Kevin Denny	Reviser	• Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 • Remove content adequately captured in the platform • Update information captured in the Division of Legal and Regulatory Support Endorsement section • Other minor administrative corrections to format and content
03	1/24/18	Kevin Denny	Reviser	• Update Final Decision section

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 23, 2019
TIME: 3:00 PM- 4:00 PM
LOCATION: WO Bldg 75 Room 2400
APPLICATION: ANDA 208702 Amendment 6
DRUG NAME: Acyclovir Cream 5%
TYPE OF MEETING: Internal meeting
MEETING CHAIR: Sarah Yim

MEETING RECORDER: Teena Thomas, Rebecca Wong

FDA ATTENDEES: (Title and Office/Division)

Raquel Tapia, Primary Reviewer (Office of Generic Drugs/Division of Clinical Review)
Sarah Yim, Director (OGD/DCR)
Carol Kim, Acting Team Leader (OGD/ DCR)
Teena Thomas, Project Manager (OGD/DCR)
Sam Raney, Team Leader (OGD/Division of Therapeutic Performance)
Rebecca Wong, Project Manager (OGD/Division of Bioequivalence II)
Anil Nair, Team Leader (OGD/DB II)
Li, Li, Primary Reviewer (OGD/DB II)
Zhang, Hongling, Tertiary Reviewer (OGD/DB II)

EXTERNAL CONSTITUENT ATTENDEES:

N/A

BACKGROUND:

This meeting was called to discuss the status of ANDA 208702 Amendment 6 (acyclovir cream, 5%) and a regulatory path forward. The applicant conducted both in vivo and vitro studies to establish BE between products. The clinical endpoint BE study (PRG-NY-14-008) failed to demonstrate sufficient assay sensitivity to definitely conclude BE and per DB, the in vitro approach was also inadequate due to an inadequate In Vitro Permeation Test (IVPT). Although the clinical endpoint BE study didn't have sufficient assay sensitivity to definitely conclude BE, the study provides comparable clinical response between products and does not raise any clinical concern from a safety perspective. Since the test formulation is Q1 (qualitatively), Q2 (quantitatively), and Q3 (Physiochemically) the same as the RLD, with acceptable IVRT data, DCR has low index of clinical concern that the proposed test formulation would not be therapeutically equivalent to the RLD. Thus, DCR is recommending approval based on the collective weight of evidence. DCR would like to discuss whether the clinical endpoint BE study can be used to mitigate the remaining uncertainty for the insufficient IVPT data to support BE and conclude therapeutic equivalence and substitutability.

MEETING OBJECTIVES:

To discuss a regulatory path forward for this ANDA.

DISCUSSION POINTS:

DCR recommends approval of this ANDA based on the totality of information in the application. Although clinical endpoint bioequivalence (BE) study PRG-NY-14-008 did not have sufficient assay sensitivity to definitively conclude BE because statistically significant superiority of Test and Reference Listed Drug (RLD) was not demonstrated over vehicle treatment alone, this is likely due to limited treatment effect size of the RLD. A vehicle effect was noted in the original reviews of the RLD and was postulated as a factor in the limited treatment effect size. As the purpose of the superiority to placebo/vehicle is only to confirm assay sensitivity of the study (i.e. that Test and RLD are BE in a study able to show a treatment effect), having a placebo/vehicle that has an effect on its own would make this endeavor more difficult, and for endpoints with such a small treatment effect size, perhaps a true placebo (i.e., a different control treatment) should be considered, if clinically feasible. In any case, the Test and RLD did appear to show a response, albeit not large enough over the vehicle to be statistically significant; and descriptive results from the study support a comparable clinical response between Test and RLD and do not raise any clinical concerns.

Although the clinical data is not adequate on its own to definitively conclude BE, in this case it is not on its own, as the application was originally submitted with an in vitro approach. That makes this case unique in that, in addition to the clinical data, the proposed formulation is qualitatively (Q1), quantitatively (Q2) the same as the RLD, with comparable physicochemical characterization (Q3) and demonstrates acceptable in vitro release (IVRT) performance. Acknowledging that the in vitro approach would ordinarily be considered incomplete without adequate in vitro permeation test (IVPT) data, IVPT is performed as a biorelevant performance test to support BE, and the in vitro approach is ordinarily done as an alternative to a clinical endpoint BE study, so there would not ordinarily be clinical data. In this case, the clinical data from Study PRG-NY-14-008 represents an extensive therapeutic experience that provides more direct information than IVPT on the clinical performance of the formulation and mitigates the remaining uncertainty in this application's in vitro approach. Consideration is taken on the context of use and risk-benefit profile of the RLD. Therefore, based on these global considerations and totality of information in the application, DCR concludes the Test and RLD are likely to be therapeutically equivalent and substitutable, and recommends approval of ANDA 208702.

Both ORS and DB agree with the DCR recommendations and with DCR providing the aforementioned justification/rationale to approve the application. DB agrees to amend their review after the DCR review is finalized and would change the recommendation to adequate deferring the final decision to DCR. Please note that the DB found applicant's IVPT inadequate due to deficiencies identified in the method development/validation and pivotal study.

DECISIONS (AGREEMENTS) REACHED:

DCR would recommend approval contingent on other Disciplines since this is a unique situation with unique elements to support bioequivalence of the proposed generic drug product. DCR would also document the rationale for recommending approval of this application even though the clinical endpoint BE study had insufficient assay sensitivity to definitively conclude BE on its own. Both ORS and DB would support DCR decision.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

N/A

ACTION ITEMS:

- DCR will complete the review with justification to support approval.
- DB will revise the bioequivalence review and defer to DCR's review to take action.

Teena Thomas

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M E M O R A N D U M

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

DATE: November 30, 2018

TO: Dale Conner, Pharm.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs

FROM: Mohsen Rajabi Abhari, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE/OSIS

SUBJECT: Routine inspections of clinical sites supporting clinical endpoint Study PRG-NY-14-008 (ANDA 208702)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of Rochester Clinical Research, Inc, Rochester, NY; New River Valley Research Institute, Christiansburg, VA; and Evanston Premier Healthcare Research, LLC, Evanston, IL.

No objectionable conditions were observed and Form FDA 483 was not issued at the close-out of any of the inspections. However, a few items were discussed at the inspection close-outs. The final inspection classification for all inspected sites is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited study PRG-NY-14-008 are reliable. Thus, I recommend that the data from Study PRG-NY-14-008 be accepted for further Agency review. In addition, the data from other studies of similar design conducted at Rochester Clinical Research, Inc, Rochester, NY; New River Valley Research Institute, Christiansburg, VA; and Evanston Premier Healthcare Research, LLC, Evanston, IL before the end of the current surveillance interval should be accepted for review without an inspection.

2. Inspected Study:

The following study was audited during the inspections:

ANDA 208702

Study Number: PRG-NY-14-008
Study Title: "A Multicenter, Double-Blind, Randomized Vehicle-Controlled, Parallel-Group Study to Compare Perrigo UK FINCO's Acyclovir Cream, 5% with ZOVIRAX® (Acyclovir) Cream 5%, and both Active Treatments to a Vehicle Control in Treatment of Recurrent Herpes Labialis"
Dates of conduct: 10/6/2014 – 4/27/2016

Site 1:
Rochester Clinical Research, Inc.
500 Helendale Rd-L20
Rochester, NY
Investigator Name: Matthew Davis

Site 2:
New River Valley Research Institute
110 Akers Farm Rd
Christiansburg, VA
Investigator Name: Mark Ringold

Site 3:
Evanston Premier Healthcare Research LLC
2500 Ridge Ave, Ste 109
Evanston, IL
Investigator Name: Jeffrey Geohas

Rochester Clinical Research, Inc. Rochester, NY
ORA investigators Benton Ketron and Karen Kosar inspected Rochester Clinical Research, Inc. from October 15-18, 2018.

New River Valley Research Institute, Christiansburg, VA
ORA investigator Eileen Bannerman inspected New River Valley Research Institute from October 29 to November 1, 2018.

Evanston Premier Healthcare Research LLC, Evanston, IL
ORA investigators Debra Boyd-Seale and Shalonda Clifford inspected Evanston Premier Healthcare Research LLC from October 11-18, 2018.

The inspections included a thorough examination of study records, case report forms (CRFs), informed consent process, protocol deviations, institutional review board approvals,

sponsor and monitor correspondence, test article accountability and storage, randomization, and adverse events.

3. Inspectional Findings

Rochester Clinical Research, Inc. Rochester, NY
At the conclusion of the inspection, ORA investigators Benton Ketron and Karen Kosar did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, the following item was discussed with the firm's management during the inspection and at close-out. The firm's response during the inspection and my evaluation follow.

Discussion item 1: The lack of required pregnancy test for Subject #3285.

Firm's Response:

During the inspection, the firm acknowledged that a pregnancy test should have been conducted and stated it was most likely an oversight by the study staff as the subject was identified as post-menopausal but not for the required length of time needed to exempt from the test.

OSIS Evaluation:

According to the study protocol, a pregnancy test should be conducted for female subjects excluding women who have been post-menopausal for at least 2 years. Subject (b) (6) was identified as post-menopausal for less than 2 years, however, the subject did not experience any AEs. Therefore, subject safety was not compromised due to the discussion item and there was no impact on the study outcome.

New River Valley Research Institute, Christiansburg, VA
At the conclusion of the inspection, investigator Eileen Bannerman did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, the following items were discussed with the firm's management during the inspection and at close-out. The firm's response during the inspection and my evaluation follow.

Discussion item 1: White out was used on the Call/Text log dated 1/28-2/9/2016.

Discussion item 2: The receiving document for the shipment of 21 kits of IP received on/about 1/20/15 lacked the Acknowledgement of Receipt signature.

Discussion item 3: Instances in which a minor subject did not sign an assent form prior to enrollment in the study. Three of these assent violations were reported as protocol deviations in the study report.

Discussion item 4: No temperature monitoring of the retain samples for the last 10 months (12/21/2017 – 10/30/2018).

Discussion item 5: Three instances in which subject reported adverse events were not documented in the eCRF.

Discussion item 6: One instance in which a concomitant medication was not reported in the eCRF.

Firm's Response:

During the inspection, the firm acknowledged the discussion items.

OSIS Evaluation:

None of the subjects who were listed in the discussion items experienced any major AEs. For discussion item 3, although assent forms were not signed, each minor initialed or signed the informed consent documents along with their parent. Therefore, subject safety was not compromised due to the discussion item and there was no impact on the study outcome.

The reserve samples were stored in a locked cabinet without temperature monitoring for 10 months. However, review of the temperature monitoring records for the locked drug storage cabinet for more than three years (October 2014 to December 2017)prior to the inspection revealed no temperature excursion. The recommended storage temperature was at room temperature (25°C (77°F)). It is not likely that there were temperature excursions beyond the recommended storage temperature. Therefore, the integrity of the reserve samples was not impacted.

Evanston Premier Healthcare Research LLC, Evanston, IL
At the conclusion of the inspection, investigators Debra Boyd-Seale and Shalonda Clifford did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

However, the following items were discussed with the firm's management during the inspection and at close-out. The firm's response during the inspection and my evaluation follow.

Discussion item 1: The key to the drug storage room was maintained in an unlocked drawer in an open area.
Discussion item 2: The retention sample was stored in an unlocked plastic container with a sample from another study.

Firm's Response:

The firm's management acknowledged the findings and changed the location of the key to the firm's director office.

OSIS Evaluation:

The reserve samples were stored in a plastic bin in a locked room. Although the key to the storage room was kept in an unlocked drawer, the ORA investigator did not identify any potential threats to access of the storage room. Therefore, the integrity of the study reserve samples was not impacted. As a corrective action, the firm changed the location of the storage key to the director office.

Discussion item 3: Documents, such as the monitoring visit notes, an updated protocol, and communication from the monitor/sponsor were missing from the regulatory binder. Additionally, the regulatory documents did not document that the name of the monitoring contractor had changed during the study.

Firm's Response:

The firm's management provided copies of the missing documents. The firm stated that the name of the monitoring contractor changed, however the same person visited the firm during the study.

OSIS Evaluation:

The firm's action in providing the missing documents is acceptable. This discussion item has no impact on the study outcome.

Discussion item 4. the clinical investigator did not follow the protocol. For example, the clinical investigator did not verify when female subjects reported a history of surgical sterilization.

Firm's Response:

The firm stated that subjects (b) (6) reported having (b) (6), but they did not provide any documents for verification. The firm's management accepted the subjects' word as a verification. The firm indicated that the sponsor did not require verification of the surgical sterilization. The firm also accepted Subject (b) (6) abstinence as a form of contraception.

OSIS Evaluation:

According to the study protocol, verification of surgical sterilization of female subjects is required. The protocol also states that abstinence only is not an acceptable form of contraception. The firm did not follow the protocol by randomizing subjects (b) (6) however the subjects did not experience any AEs. Therefore, subject safety was not compromised due to the discussion item and there was no impact on the study outcome.

Discussion item 5: The firm did not maintain tracking forms of the shipment of investigational product.

Firm's Response:

The firm provided the email communication and shipment label from Investigators Research Group, Brownsburg, IN that shipped the investigational product.

OSIS Evaluation:

The firm's corrective action is acceptable. This discussion item has no impact on the study outcome.

4. Conclusion:

After reviewing the inspectional findings, I conclude the data from the audited study are reliable. Therefore, I recommend that the data from Study PRG-NY-14-008 (ANDA 208702) be accepted for further review. In addition, studies of similar design conducted at Rochester Clinical Research, Inc, Rochester, NY; New River Valley Research Institute, Christiansburg, VA; and Evanston Premier Healthcare Research, LLC, Evanston, IL before

the end of the current surveillance interval should also be accepted for review by the Agency without an inspection.

Mohsen Rajabi Abhari, Ph.D.
Pharmacologist

Final Classification:

NAI Rochester Clinical Research, Inc.
Rochester, NY
FEI #: 3002288819

NAI New River Valley Research Institute,
Christiansburg, VA
FEI#: 3009279437

NAI Evanston Premier Healthcare Research LLC,
Evanston, IL
FEI#: 3011654749

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin/Rajabi
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/Ketron/Kosar/Bannerman/Boyd-Seale/Clifford/
ORABIMOE.Correspondence@fda.hhs.gov
Draft: MR 11/28/2018
Edit: AL 11/29/2018; AD 11/30/2018

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL ENDPOINT/ANDA 208702

OSIS File #: BE 8064 (ANDA 208702)

FACTS: 11837788

Mohsen Rajabi-abhari -S

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Date: 2018.11.30 15:01:31 -05'00'

Mohsen Rajabi Abhari, Ph.D.

Amanda E. Lewin -S

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Amanda Lewin Ph.D.
(signing for Gopa Biswas, Ph.D.)

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Arindam Dasgupta, Ph.D.

REVIEW of a REQUEST FOR CONSULTATION
OGD Office of Research and Standards, Division of Therapeutic Performance

To:	**Ethan Stier, Ph.D., R.Ph.** **Director, Division of Bioequivalence II (DBII)** **Office of Bioequivalence, Office of Generic Drugs**
Re:	**ANDA 208702**
Request for Consultation:	**GDRP #17166989**
Drug Products:	**Acyclovir Cream, 5 % w/w**
Sponsor:	**Perrigo UK Finco Ltd Partnership**
Submission Dates:	**January 7, 2016 (Original-1)** **August 24, 2017 (Original-1, Amendment-6)**
GDUFA Goal Date:	**February 4, 2019 (Original-1, Amendment-6)**
Mid Cycle Date:	**June 14, 2018 (Original-1, Amendment-6)**
Date of Consult Review:	**May 14, 2018 (Original-1, Amendment-6)**
Consultant:	**Priyanka Ghosh, Ph.D.** **Division of Therapeutic Performance** **Office of Research and Standards, Office of Generic Drugs**
Through:	**Sam Raney, Ph.D.** **Team Lead (Acting)** **Division of Therapeutic Performance** **Office of Research and Standards, Office of Generic Drugs** **Markham Luke, M.D., Ph.D.** **Director, Division of Therapeutic Performance** **Office of Research and Standards, Office of Generic Drugs**

Reason for Consultation

Perrigo UK Finco Ltd Partnership (Perrigo) submitted abbreviated new drug application (ANDA) 208702 for acyclovir cream, 5% on 1/7/2016. The reference listed drug (RLD) for the ANDA submission is Zovirax® (acyclovir) topical cream, 5% (NDA 021478; approved on 12/30/2002) manufactured by Valeant International Bermuda.

The draft product specific guidance (PSG) for acyclovir topical cream, 5% which had been recommended in December of 2014 and was available at the time of the ANDA submission in January 2016 recommended a bioequivalence (BE) study with clinical endpoint, and stated that an in vitro BE approach

was being developed by the Agency, but did not provide specific recommendations regarding this approach.

In the original submission in January, 2016, Perrigo requested a waiver of in vivo BE studies for the proposed acyclovir topical cream, 5%. To support its request, the firm submitted the following information: 1) test product formulation; 2) comparative physicochemical characterization of the test and RLD formulations; 3) a comparative in vitro drug release test (IVRT) of acyclovir from the test and RLD formulations and 4) a comparative in vitro skin permeation test (IVPT) of acyclovir from the test and RLD formulations. The current request for consultation relates to the IVPT study conducted within the scope of the weight of evidence based in vitro approach for establishing BE that Perrigo proposed in the original submission in 2016.

The current revised draft PSG for acyclovir topical cream was published in December 2016[1] and provides detailed recommendations for establishing BE between a proposed acyclovir topical cream, 5% test product and Zovirax® (acyclovir) topical cream, 5% (RLD) using an in vitro option. The PSG recommends the following tests:

"A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry ANDA Submissions– Refuse-to-Receive Standards, Revision 1 (May 2015).
B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

a. Assessment of appearance
b. Analysis of the polymorphic form in the drug product
c. Analysis of particle size distribution and crystal habit with representative microscopic images at multiple magnifications.
d. Analysis of the rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms.
e. Analysis of specific gravity, water activity, pH and any other potentially relevant physical and structural similarity characterizations.

C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.
D. ***The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method."***

The DBE II review of the original submission (conducted after the publication of the PSG in December 2016),[2] concluded that the IVPT study submitted by Perrigo was inadequate due to multiple deficiencies in the IVPT method development, method validation, analytical method and conduct of pivotal study. The IVPT study (PER-AR-005-15-R00) was conducted at (b) (4) In response to the deficiencies communicated in the complete response (CR) letter dated 3/17/2017,[3] Perrigo submitted an amendment on 8/24/2017 (Amendment-6). According to the current request for consultation

[1] Draft Guidance on Acyclovir Cream
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428195.pdf.
(recommended December 2014; revised in December 2016). Last accessed 05/01/2018
2 ANDA 208702 Division of Bioequivalence Review by Li, Li dated 2/2/2017
3 ANDA 208702 Complete Response by Mckan, Denise Toyer dated 3/17/2017

Perrigo did not submit any new data for the IVPT study in Amendment-6.[4] Perrigo did respond to some of the questions raised in the CR letter, however DB II found the responses to be unacceptable.

Therefore, on 03/14/2018, the Division of Bioequivalence (DBII) sent the current request for consultation to Office of Research Standards (ORS) to seek advice regarding the acceptability of the applicant's IVPT study design. The study (PER-AR-005-15-R00) was designed to use 6 replicate skin sections for each treatment group (reference and test) from 3 donors. DB II has the following questions regarding IVPT method development/validation, sample analysis by LC-MS/MS and pivotal study:

Questions in the Request for Consultation:

IVPT method

- (b) (4)
- The skin surface temperature was controlled (b) (4) and the skin surface temperature was not measured.
- The study dose used for the IVPT study was 5 mg/cm^2 which is within the PSG recommended dose range of 5-15 mg/cm^2. However, the applicant did not evaluate the IVPT method discrimination using different dose amounts of Acyclovir Cream.
- (b) (4)
- The acceptance criterion for skin integrity test was set up as of electrical resistance value (b) (4) the reading of the diffusion medium. According to the applicant, this acceptance criterion was set up based o (b) (4) previous experience on skin test.
- The applicant did not measure the skin thickness for each skin section during IVPT study.

Question: Are the applicant's IVPT method conditions acceptable? If not acceptable, any rational or suggestions that DBII can provide to the applicant regarding IVPT method conditions?

IVPT method validation

- IVPT method precision and reproducibility
- IVPT Recovery, mass balance and dose depletion

The applicant evaluated the above validation parameters using the data obtained from pilot study. However, its pilot study included only 6 replicate skin samples from one donor; therefore, there was no inter-donor validation data.

- IVPT method discrimination, sensitivity and selectivity
- IVPT method robustness

The applicant stated that its IVPT method is similar to the method in the literature, therefore, there is no need to evaluate its method discrimination, and sensitivity and selectivity as these parameters were already established in the literature. The applicant also claimed that its IVPT method is suitable considering that 1) the variation between and within skin donors is greater than any variability in the other testing parameters, 2) there is only a (b) (4) of acyclovir penetrating to the receptor medium,

[4] GlobalSubmit Review ANDA 208702 - Sequence 0005 - 1.2 Cover Letters - \\cdsesub1\evsprod\anda208702\0005\m1\us\1-2-1-cover-letter-0005.pdf

3) the test and reference products were evaluated in the same run, 4) the permeation results are comparable to those in the literature.

DBII found the applicant's response unacceptable, and will request the applicant to evaluate the IVPT method per the PSG.

Question: Does the applicant's IVPT method validation using pilot study data (with 1 donor only) acceptable for IVPT precision, reproducibility, recovery and mass balance dose depletion? If not acceptable, any further information/suggestions we could provide to the applicant regarding the IVPT method validation?

IVPT Analytical Method

(b) (4)

IVPT Pivotal Study

The applicant's IVPT study included skin samples from 3 donors, 6 skin sections per donor. In response to the deficiency comment that the IVPT study should be adequately powered, the applicant stated the following justifications:

- IVPT study is a supporting evidence to the similarity of in vitro release performance between Test and reference products.
- The applicant's IVRT study with 3 lots of test and reference met the acceptance criteria
- (b) (4)
- To adequately power the study, more than 40 donors would be needed.
- In the applicant's IVPT study, the total absorption of the T and R appeared to the same; T and R have similar flux and mass distribution pattern, therefore, the rate and extent of permeation of acyclovir through skin were comparable for T and R.
- (b) (4)
- The applicant conducted mass balance and drug distribution studies for both pilot and pivotal studies.
- The applicant seems to be reluctant to repeat the IVPT study.

Question: The applicant's above justification that its IVPT pivotal study was adequately powered is not acceptable. Can DTP provide any rational/suggestions to substantiate our comment that the applicant's response is unacceptable?
Are the drug distribution and mass balance data needed for both pilot and pivotal studies? Or only for pilot study? Should we let the applicant know that we are only looking at the permeation results for the pivotal study? Is there any further information/suggestions we can provide to the applicant regarding the IVPT study design and execution?

DBII proposal and Overall questions to DTP related to IVPT study

- Based on the IVPT data in the applicant's original submission, and the applicant's response in the amendment of August 24, 2018, DBII found the applicant's IVPT study inadequate. DBII will request the applicant to develop and validate its IVPT method per the PSG, and repeat the IVPT study ensuring that the IVPT study is adequately powered.

- Please provide any additional rational, comments or suggestions that may be included in the deficiency comment for the applicant's IVPT method development/validation, analytical method and pivotal studies.

Subsequently on 4/15/2018, Perrigo submitted A MULTICENTER, DOUBLE-BLIND, RANDOMIZED VEHICLE-CONTROLLED, PARALLEL- GROUP STUDY TO COMPARE PERRIGO UK FINCO'S ACYCLOVIR CREAM, 5% WITH ZOVIRAX® (ACYCLOVIR) CREAM 5%, AND BOTH ACTIVE TREATMENTS TO A VEHICLE CONTROL IN TREATMENT OF RECURRENT HERPES SIMPLEX LABIALIS.[5] Based on a phone call between Rebecca Wong (DB II) and (b) (4) it was clarified that OB has made the decision to evaluate both the in vitro approach (including the IVPT study) and the in vivo clinical end point study for establishing BE for the proposed acyclovir topical cream 5% from Perrigo.

Background for Consultation

The RLD product is Zovirax® (acyclovir) topical cream, 5%, initially approved on December 30, 2002 under New Drug Application (NDA) 021478. It is indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older. Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 and varicella-zoster virus.[6] There are currently no unexpired patents and no unexpired exclusivities for this product in the Orange Book database, and yet, there are currently no approved therapeutically equivalent generic drug products available referencing this RLD.[7,8]

The revised PSG for Acyclovir Cream (Dec 2016)[1] retains the recommendations in the original PSG (Dec 2014) for the clinical endpoint BE study, with a revision to the recommended statistical analysis. However, since the statistical consult during the revision process confirmed that the number of patients

[5] GlobalSubmit Review ANDA 208702 - Sequence 0006 - Cover Letter 0006 - April 5, 2018
[6] DARRTS records for NDA 021478, including in-use labeling revised 06/2015.
[7] Patent and Exclusivity information in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations online database accessible at http://www.accessdata fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=021478&Appl_type=N. Last accessed 4/25/2018
[8] Therapeutic Equivalents information in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations online database accessible at http://www.accessdata fda.gov/scripts/cder/ob/search_product.cfm. Last accessed 4/25/2018

required to demonstrate BE with a clinical endpoint BE study may be unfeasibly large, the revision included an alternative set of recommendations for demonstrating BE using an in vitro option. To facilitate the receipt of ANDAs referencing this RLD (Zovirax® (acyclovir) cream 5%; NDA 021478) that would be sufficiently complete and of suitable quality relative to the expectations of the relevant review divisions, the review divisions collaborated closely with the Division of Therapeutic Performance during the development of the in vitro option, and the revised BE Guidance contains substantial detail relating to the recommendations for development, validation, conduct and analysis for each in vitro test criterion.

Below is a summary of relevant recommendations in the PSG[1] related to the design and conduct of IVPT studies, with corresponding deficiencies observed with Perrigo's pilot and pivotal studies that are expected to impact the conclusions from the study:

1. **Recommendation in PSG:** The IVPT pivotal study should utilize a balanced design directly comparing the test and RLD products on skin from the same set of donors, using a single, un-occluded dose in the range of 5-15 mg cream/cm^2 and sufficient number of donors required to adequately power the IVPT pivotal study..... It is the responsibility of the applicant to determine the number of donors required to adequately power the IVPT pivotal study, however, a minimum of 4 dosed replicates per donor per treatment group (RLD or test) is recommended.

According to the study report,[9] Perrigo conducted a pivotal study using a balanced design directly comparing the test and RLD products on skin from 3 donors, and, 6 replicates from each donor, using a single dose of 5 mg cream/cm^2. (b) (4)

(b) (4)

The demonstration of an equivalent rate and extent of bioavailability (BA) of acyclovir from the test and RLD products, evaluated by a validated IVPT method, mitigates the risk that any unknown failure modes (that may not be evaluable by Q1/Q2/Q3 sameness and an IVRT equivalence criteria) may lead to differences in BA or BE for the test product with respect to the RLD product. A substantial body of evidence exists indicating that IVPT results correlate with and are predictive of in vivo BA and/or BE.[10, 11, 12] An IVPT study is recommended for acyclovir topical cream, 5% since the metamorphosis of the cream and resultant drug delivery may be different due to differences in manufacturing processes which may or may not be captured by the small set of Q3 characterizations and an IVRT study. Therefore, an IVPT study, conducted with appropriate controls as recommended in the PSG[1] is critical for establishing the BE of a proposed acyclovir topical cream, 5% drug product using the in vitro approach.

Differences in dosing technique or occlusion of the dosing chamber during an IVPT study may alter the metamorphosis of the dosage form on the skin. The drying and metamorphosis of the test and RLD formulations is expected to alter the permeation of the drug across the skin when used by a patient, in a manner that is compared and characterized during the IVPT study. A key function of the

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[9] GlobalSubmit Review ANDA 208702 - Sequence 0000 - 5.3.1.2 [[Study ID]] - [[Study Title]] - PER-AR-005-15-R00 - Analytical Report for Characterization of the Percutaneous Absorption of Acyclovir from Acyclovir Cream (USP 5% w/w) Formulations Dosed on Human Donor Skin Using the Finite Dose In Vitro Permeation Test Model

[10] Franz et al. (2009) Use of Excised Human Skin to Assess the Bioequivalence of Topical Products. Skin Pharmacol Physiol. 22:276–286

[11] Lehman et al. (2011) Percutaneous Absorption in Man: In vitro-in vivo Correlation. Skin Pharmacol Physiol. 24:224–230

[12] Raney et al. (2015) Pharmacokinetics-Based Approaches for Bioequivalence Evaluation of Topical Dermatological Drug Products. Clin Pharmacokinet. 54:1095–1106

IVPT study is to mitigate the risk that that there could be an in vivo difference in the rate and extent of acyclovir permeation that might result from differences in the metamorphosis of the cream from a finite dose applied on the skin and maintained at the physiological skin temperature. The occlusion of the cells during an IVPT study inhibits the drying and metamorphosis of the cream. This study design may have been considered beneficial because occlusion is known to enhance the permeation of drugs through the skin, and occlusion prevents the drying of the dosage form which can help to sustain drug delivery. Collectively, this can improve the ability to quantify poorly permeating drugs in the receptor solution. However, these strategies undermine the ability of the IVPT method to be discriminating to differences between the Test and RLD products that may cause them to exhibit a different rate and extent of drug delivery when used by patients.

Therefore, it is not appropriate to conduct the IVPT BE study comparing the test and reference product under occlusion. As noted in Amendment-6, Perrigo has access to acyclovir permeation data generated within the scope of the GDUFA regulatory science program which establishes that it is feasible to conduct a BE study for acyclovir topical cream 5% without occlusion of the donor chambers.

According to the PSG, it is the responsibility of the applicant to determine the number of donors required to adequately power the IVPT pivotal study based on a pilot study in sufficient number of donors and replicates. Perrigo claims that they conducted "A pilot study based on a single donor and one test formulation". A permeation study using what appears to be one set of conditions on a single donor using a single formulation can scarcely even be considered a method development study, and does not address the several objectives that should be addressed by a pilot study, as recommended in the PSG[1]. Therefore, the current submission lacks both, an acceptable pilot study and an acceptable pivotal study, as recommended in the PSG[1], and Perrigo should be advised that if it intends to demonstrate BE using an in vitro approach then it should follow the detailed recommendations in the PSG[1].

Perrigo claimed that more than 40 donors will be needed to conduct a pivotal IVPT study for establishing BE, and therefore such a study is not feasible. However, based on the information available to both Perrigo and the Agency, while the number of donors needed to adequately power a IVPT study depends on the variability observed in the associated method, study conditions, relevant to the methodologies utilized by a particular laboratory, multiple datasets from independent research groups supported by GDUFA research awards have established that it is feasible to establish BE in an IVPT study using as few as 6 donors. The estimate of 40 donors calculated by Perrigo could be a consequence of having too few donors in the empirical dataset used to make perform the calculations.

2. **Recommendation in PSG:** IVPT method development studies should support the selection of the dose amount utilized in the study, even if within the recommended range. The dose should be justified for each IVPT system based upon studies performed during IVPT method development. IVPT method development studies should also be used to select of an appropriate sampling schedule and duration.

According to the study report,[13] Perrigo conducted a pivotal study using a balanced design directly comparing the test and RLD products on skin from 3 donors, and, 6 replicates from each donor, using a single dose of 5 mg cream/cm^2. Although the dose is within the recommended range of 5-15 mg cream/cm^2, Perrigo didn't conduct a proper dose ranging study to evaluate the sensitivity of their

[13] GlobalSubmit Review ANDA 208702 - Sequence 0000 - 5.3.1.2 [[Study ID]] - [[Study Title]] - PER-AR-005-15-R00 - Analytical Report for Characterization of the Percutaneous Absorption of Acyclovir from Acyclovir Cream (USP 5% w/w) Formulations Dosed on Human Donor Skin Using the Finite Dose In Vitro Permeation Test Model

method. According to Amendment-6,[4] the dose was selected based on OECD guidelines. However, it is critical that any IVPT method used for evaluation of BE should be sensitive in the dose range being used to conduct the pivotal IVPT study. Sensitivity in such a situation is the ability to detect changes in the permeation, as a function of dose. If the IVPT method consistently identifies higher or lower rates of permeation with increased or decreased dose, respectively, the IVPT method may be considered sensitive. Therefore, although the dose utilized by Perrigo appears to be at the lower end of the recommended range, a dose ranging study is recommended to make sure that the IVPT method being used is sensitive to potential differences in BA between the Test and RLD products.

3. **Recommendation in PSG:** IVPT method validation should include, at a minimum, qualification of the apparatus, skin, receptor solution, environmental conditions, dosing, sampling, and other IVPT study variables utilized in the IVPT pivotal study.

a. **IVPT Apparatus Qualification:** According to the study report, Perrigo used a (b) (4) (b) (4) for the IVPT studies. (b) (4) (b) (4)

There are several diffusion cell apparatuses in common use across the industry. The two fundamental designs are a vertical diffusion cell (also known as a Franz Cell) and a flow-through diffusion cell (also known as a Bronaugh Cell). The essential difference between the two designs is the frequency with which the receptor fluid beneath the skin is refreshed to optimize sink conditions - an ideally infinite capacity to receive/dissolve drug that has permeated into and through the skin. In the flow-through cell, the receptor fluid is continuously flowing under the skin at a slow rate to refresh a small volume at high frequency. In the Franz Cell, a large volume is sampled and refreshed at a lower frequency determined by the sampling time points. Both diffusion cell are potentially suitable for the performance of IVPT studies. The Logan diffusion cell system is relatively new and not as well understood as PermeGear's flow through (automatic sampling) or Franz diffusion cells (manual sampling).

Therefore, Perrigo should be requested to validate the IVPT method (b) (4) (b) (4)

(b) (4)

(b) (4) therefore it is critical that a method used for establishing BE is validated on the exact same test system (same apparatus, dose amount and application technique, sampling timepoints and procedures, and other study parameters).

b. **IVPT Membrane (Skin) Qualification:** The consult review from DTP for ANDA (b) (4)

c. **IVPT Receptor Solution Qualification:** The PSG[1] recommends that qualification of the receptor solution should include the composition and pH of the receptor solution utilized for the IVPT study in relation to its compatibility with the skin as well as the solubility and stability of acyclovir. The minimum solubility of acyclovir in the IVPT receptor solution should be empirically determined in triplicate with acyclovir dissolved to saturation in the receptor solution, to a concentration exceeding the highest sample concentration in the IVPT pivotal study, ideally by an order of magnitude. (b) (4)
(b) (4)

d. **IVPT Receptor Solution Sampling Qualification:** The PSG[1] recommends that the entire receptor solution volume be removed and replaced at each time point to provide optimal solubility sink conditions when a vertical diffusion cell is used. (b) (4)
(b) (4)

(b) (4)

e. **IVPT Receptor Solution Sample Analytical Method Validation:** Perrigo used (b) (4) for quantification of acyclovir in the skin and permeation samples. (b) (4) Therefore, Perrigo should be recommended to develop and validate a method for the quantification of acyclovir in the receptor solution in a manner compatible with the PSG[1], which itself references the FDA Draft Guidance for Industry on Bioanalytical Method Validation (Revision 1; September 2013)16.

(b) (4)

f. **IVPT Environmental Control:** According to the study report,[4] the Franz Diffusion Cell system used in the study (b) (4) However, the DB review[2] indicates that the temperature of the surface of the skin was not measured during the IVPT studies therefore Perrigo should be recommended to measure the temperature directly at the surface of the skin.

g. **IVPT Pilot Study:** Following the IVPT method development studies, a pilot IVPT study comparing the test and RLD products is recommended, to estimate the number of donors required for the IVPT pivotal study. A pilot IVPT study performed with multiple skin donors and a minimum of 4 replicate skin sections per donor per treatment group is recommended. The pilot study can be used to calculate the number of donors required to adequately power a pivotal study for establishing BE. The pilot study currently conducted by Perrigo in one donor and 6 replicates using a single formulation is not appropriate to serve the purpose of a pilot study as recommended in the PSG[1], therefore Perrigo should be recommended to repeat both the pilot and pivotal studies using the approach recommended in the PSG[1]. The concentration of acyclovir in the skin and the mass balance of acyclovir based on concentration in the different layers of the skin is not qualitatively evaluated for establishing BE because it provides data only at one point in time, and does not support an adequate comparison of the pharmacokinetics (the rate) at which the acyclovir becomes available in the skin.

4. **Recommendation in PSG:** Data analysis during pivotal study should be based on the statistical recommendations developed for using IVPT as a method for establishing BE.

   Perrigo has currently used the means from each donor to obtain the across donor population mean

[16] FDA Draft Guidance for Industry on Bioanalytical Method Validation (Revision 1; September 2013). Accessible at: https://www fda.gov/downloads/drugs/guidances/ucm368107.pdf. Last accessed 05/14/2018.

± SD for statistical analysis. The data analysis used by Perrigo is different from the recommendations in the PSG[1] and are not suitable to evaluate BE. Perrigo should be recommended to use the data analysis recommendations in the PSG[1] for the design, conduct, and analysis of IVPT studies.

The review of the study protocol also indicates that the "outlier" criteria was developed after the completion of the IVPT study instead of being pre-specified in the protocol, the outliers appear to potentially be justifiable from a scientific perspective based on the difference in absolute values between the "outlier" and other values for the same product in the same donor, however, there is insufficient detail in the information provided to assess properly whether the removal of these "outliers' is justified. Also, the Scaled Average BioEquivalence (SABE) statistical analysis can be robust to the influence of outliers, so it would be advisable to perform a SABE analysis without any skin sections being removed from the dataset and to compare the conclusion regarding BE.

Response to Questions in the Request for Consultation

1. **QUESTION: Are the applicant's IVPT method conditions acceptable? If not acceptable, any rational or suggestions that DBII can provide to the applicant regarding IVPT method conditions?**

RESPONSE:

No, the following conditions **are not acceptable** for the pilot and pivotal BE studies due to the reasons summarized below:

- (b) (4)

(b) (4)

- **The study dose used for the IVPT study was 5 mg/cm^2 which is within the PSG recommended dose range of 5-15 mg/cm^2. However, the applicant did not evaluate the IVPT method discrimination using different dose amounts of Acyclovir Cream.**

  It is critical that any IVPT method used for evaluation of BE should be sensitive and discriminating to changes in the rate and extent of drug delivery. The sensitivity of an IVPT method can be demonstrated based upon its ability to detect changes in the permeation profile as a function of dose. If the IVPT method consistently identifies higher or lower rates of permeation with increased or decreased dose, respectively, the IVPT method may be considered sensitive. Therefore, although the dose utilized by Perrigo is within the recommended range, there is no information provided to demonstrate that the specific study design and methodologies associated with their IVPT conduct are discriminating using their selected dose; for example, it is unclear whether all the results are predominantly based upon a measurement of the "interfering"

compound that is confounding their analytical method. A dose ranging study is recommended to make sure that the IVPT method being used is sensitive.

The following conditions **may be acceptable** for the pilot and pivotal BE studies if adequate justification is provided due to the reasons summarized below:

- **The applicant did not** [redacted] Therefore, Perrigo should be recommended to utilize the methods for full removal of the receptor solution at each time point, as specified in the PSG[1].

- **The acceptance criterion for skin integrity test was set up as of electrical resistance value** [redacted] **the reading of the diffusion medium. According to the applicant, this acceptance criterion was set up based on** [redacted] **previous experience on skin test.**

  Perrigo used an electrical impedance/conductance test, which may be acceptable, but the criteria for determining whether or not a skin section has a normal barrier integrity is not supported by data to substantiate that the cutoff discriminates between normal and abnormal skin sections. Perrigo should be recommended to submit such supporting analyses, or, at the least, to submit data from all skin sections mounted for the study, including those that failed the cutoff criteria.

- **The applicant did not measure the skin thickness for each skin section during IVPT study.**

  Perrigo provided a range of skin thickness for the skin sections used, which may be acceptable as long as there are no significant differences in the thickness of the skin sections used for the test product treatment group compared to the reference product treatment group. Therefore, Perrigo should be recommended to either submit data from all skin sections used in the study or justify how the skin sections were assigned for the test and reference product to prevent bias.

- **The skin surface temperature was controlled** [redacted] **and the skin surface temperature was not measured.**

[redacted]

[redacted] Perrigo should be recommended to measure the temperature at the surface to accurately characterize the control of the IVPT test system.

2. **QUESTION**: ***Does the applicant's IVPT method validation using pilot study data (with 1 donor only) acceptable for IVPT precision, reproducibility, recovery and mass balance dose depletion? If not acceptable, any further information/suggestions we could provide to the applicant regarding the IVPT method validation?***

RESPONSE: No, Perrigo's method "validation" using pilot study data (with 1 donor and 6 replicates and a single formulation) is not an acceptable dataset with which to demonstrate IVPT precision, reproducibility, recovery, mass balance and dose depletion. Perrigo should be requested to validate the IVPT method according to the recommendations in the PSG[1], in order to adequately develop, control, and validate an IVPT method. [redacted]

3. **QUESTION**: ***The interference peak in the IVPT samples appears to be significant relative to the measured acyclovir concentrations in the diffusion media. Are there any interference peaks at the RT of acyclovir present in the FDA funded IVPT studies with similar analytical method using LC-MS/MS?***

RESPONSE: No, there were no interference peaks present at the RT of acyclovir in the FDA funded IVPT studies, which used analytical methods based upon HPLC UV. Therefore, Perrigo should be recommended to develop a valid (selective) for the quantification of acyclovir in the IVPT receptor solution samples. Also, as stated in the PSG[1], a non-dosed control should be included in the IVPT study to ensure that acyclovir concentrations monitored in the receptor solution are specifically associated with the dose applied in the IVPT pivotal study, and not associated with acyclovir contamination in the skin from that donor, which might permeate into the receptor solution during the study. Quantification of (the absence of) acyclovir in the pre-dose "zero" sample, and in samples from the non-dosed control skin section, may be used to mitigate the risk of such potential contamination or signal interference associated with each skin section and/or each diffusion cell. Otherwise, in the absence of such demonstrated selectivity of the quantification of acyclovir, the false signal for acyclovir may be substantial, and may be similar between test and reference treatment groups, such that the rate and extent to which "acyclovir" becomes available would erroneously appear comparable.

4. **QUESTION**:

IVPT Pivotal Study

The applicant's IVPT study included skin samples from 3 donors, 6 skin sections per donor. In response to the deficiency comment that the IVPT study should be adequately powered, the applicant stated the following justifications:

- IVPT study is a supporting evidence to the similarity of in vitro release performance between Test and reference products.
- The applicant's IVRT study with 3 lots of test and reference met the acceptance criteria
- The permeation of acyclovir into receptor medium is only 0.1%.
- To adequately power the study, more than 40 donors would be needed.
- In the applicant's IVPT study, the total absorption of the T and R appeared to the same; T and R have similar flux and mass distribution pattern, therefore, the rate and extent of permeation of acyclovir through skin were comparable for T and R.
- (b) (4)
- The applicant conducted mass balance and drug distribution studies for both pilot and pivotal studies.
- The applicant seems to be reluctant to repeat the IVPT study.

The applicant's above justification that its IVPT pivotal study was adequately powered is not acceptable. Can (b) (4) provide any rational/suggestions to substantiate our comment that the applicant's response is unacceptable? Are the drug distribution and mass balance data needed for both pilot and pivotal studies? Or only for pilot study? Should we let the applicant know that we are only looking at the permeation results for the pivotal study? Is there any further information/suggestions we can provide to the applicant regarding the IVPT study design and execution?

RESPONSE: According to the PSG[1], it is the responsibility of the applicant to determine the number of donors required to adequately power the IVPT pivotal study based on a pilot study using a sufficient number of donor and replicates (for example, six donors with 4 replicates each per treatment group). Perrigo claims that they conducted "A pilot study based on a single donor and one test formulation", however, in the opinion of the consultation reviewer a permeation study on a single donor using a single formulation is, at best, a method development study rather than a pilot study, as a pilot study is described in the PSG[1]. Therefore, the current submission lacks both, a suitable pilot study and a valid pivotal study. Perrigo should be recommended to conduct both the pilot and pivotal IVPT studies in accordance with recommendations in the PSG[1] in order for the results of the well-controlled, valid IVPT BE study to support a demonstration of BE.

It is also advisable that the dataset to use to calculate the number of donors needed for the pivotal study be developed based on recommendations in the PSG[1], because estimates based upon a very small sample size (e.g., only 3 donors) may substantially inflate the estimate. Perrigo claimed that more than 40 donors would be needed to conduct a pivotal IVPT study for establishing BE, and therefore that such a study is not feasible. However, Perrigo's assertions are contradicted by information available to the Agency, much of which has been presented at public meetings and workshops. Multiple other research groups have demonstrated the feasibility of the IVPT studies recommended in the PSG[1].

The concentration of acyclovir in the skin and the mass balance of acyclovir based on concentration in the different layers of the skin is not qualitatively evaluated for establishing BE because it provides data only at one point in time, and does not support an adequate comparison of the pharmacokinetics (the rate) at which the acyclovir becomes available in the skin.

Notably, the results from an IVPT BE study can support a demonstration of BE within the context

of other comparative product characterizations, which, collectively, mitigate the risk of relevant failure modes for bioequivalence. In the absence of an acceptable demonstration of BE using an IVPT study, the risks of relevant failure modes for bioequivalence are not adequately mitigated.

DBII proposal and Overall questions to DTP related to IVPT study: Based on the IVPT data in the applicant's original submission, and the applicant's response in the amendment of August 24, 2018, DBII found the applicant's IVPT study inadequate. DBII will request the applicant to develop and validate its IVPT method per the PSG, and repeat the IVPT study ensuring that the IVPT study is adequately powered. Please provide any additional rational, comments or suggestions that may be included in the deficiency comment for the applicant's IVPT method development/validation, analytical method and pivotal studies.

RESPONSE: DTP agrees with DBII position. In this case, the IVPT method appears to have been inadequately developed, inappropriately implemented, insufficiently qualified and validated, and inconclusively analyzed. The dataset is very small, highly variable, apparently insensitive and not even selective for acyclovir. The applicant should be recommended to develop and validate its IVPT method per the PSG[1], and repeat the pivotal IVPT study ensuring that the IVPT study is adequately powered. Please see DTP's response to the preceding questions for additional supporting reasons, comments and suggestions.

M E M O R A N D U M

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

DATE: August 30, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Xiaohan Cai, Ph.D.
Visiting Associate
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Young Moon Choi, Ph.D.
Deputy Director (Acting)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR: analytical inspection conducted at Perrigo Company, Parsippany, NJ, for ANDA 208702

Recommendations:

The Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) conducted an inspection at Perrigo Company, Parsippany, NJ. A study conducted by Perrigo Israel Pharmaceuticals, Ltd., Yeruham, Israel for ANDA 208702 was audited. At the conclusion of the inspection, a Form FDA 483 was issued with three observations that are discussed in the Inspection section of this review.

A key issue was the absence of representative reserve samples for reference listed drug (RLD) lot E3001 and uncertainty regarding whether reserve samples from RLD lot A4002 were representative of RLD lot A4002 that was used in the in vitro release test (IVRT). Because the site did not follow the applicable rules and regulations on reserve samples for RLD lots E3001 and A4002, the authenticity of RLD lots E3001 and A4002 tested in study 68024 cannot be confirmed. Therefore, this reviewer concludes that the analytical data from the in vitro release tests using RLD lots

M E M O R A N D U M

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

DATE: 7/18/2016

TO: Office of Bioequivalence
Office of Generic Drugs

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

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: ANDA 208702

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

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

Nicola M. Nicol -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola M. Nicol -S
Date: 2016.07.19 09:49:44 -04'00'