CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 209190

Name: Lidocaine (patch), 5%

Sponsor: Institute Biochimique SA

Approval Date: April 30, 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA209190Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

APPROVAL LETTER

ANDA 209190

ANDA APPROVAL

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 14, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Lidocaine Patch 5%.

Reference is also made to the complete response letter issued by this office on May 3, 2019, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Lidocaine Patch 5% to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Lidoderm Patch 5%, of Teikoku Pharma USA, Inc.

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

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

REPORTING REQUIREMENTS

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

date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

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 https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
CAPT, USPHS
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).

Catherine Poole

Digitally signed by Catherine Poole
Date: 4/30/2020 12:20:59PM
GUID: 5407887a000a1c0c26055eafb8e3258a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

LABELING

Lidocaine Patch 5 % - Patch Label

100 mm

143mm

(b) (4)

cut along dotted line

Lidocaine
Patch 5%

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive)
in an aqueous base.
Methylparaben and propylparaben as preservatives.

USUAL DOSAGE: Apply up to 3 patches. See package insert for complete prescribing information.

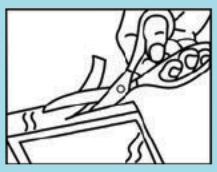
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

WARNING: Keep used and unused patches out of the reach of children, pets and others.

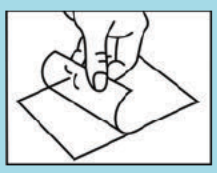
R_x Only
1 Patch (10 cm x 14 cm)

Marketed by:
Rhodes Pharmaceuticals L.P. Coventry, RI 02816
Manufactured by:
Altergon Italia Srl, Morra de Sanctis, Avellino 83040, Italy

DIRECTIONS FOR USE
Do not store patch outside the sealed envelope.

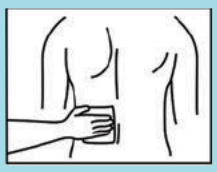


Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.



Remove the transparent release liner (clear plastic backing) before application of patch to the skin.

Apply immediately after removal from the protective envelope.



Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over Lidocaine patches is not recommended.

Lidocaine patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get them.

303193-0A

2 03 4285-8118-30 3

LOT:

EXP:

143 mm

PDDIE-339 Rev 2
Lidocaine Carton

Rx Only

NDC 42858-118-30
Lidocaine
Patch 5%

Rhodes

NO VARNISH

NDC 42858-118-30
Lidocaine
Patch 5%

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.

USUAL DOSAGE:
Apply up to 3 patches. See package insert for complete prescribing information.

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

WARNING:
Keep used and unused patches out of the reach of children, pets and others.

30 Patches

30 Envelopes
Containing 1 Patch Each

Marketed by: Rhodes Pharmaceuticals L.P., Coventry, RI 02816
Manufactured by: Altergon Italia Srl, Morra de Sanctis, Avellino 83040, Italy

Rhodes

Rx Only

NO VARNISH

Rx Only

NDC 42858-118-30
Lidocaine
Patch 5%

Rhodes

NO VARNISH

NDC 42858-118-30
Lidocaine
Patch 5%

DIRECTIONS FOR USE
Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.

Remove the transparent release liner (clear plastic backing) before application of patch to the skin.

Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patch if irritation occurs.

Placement of external heat sources, such as heating pads or electronic blankets, over Lidocaine patches is not recommended.

Lidocaine patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming, or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

N 3 42858-118-30 9

303192-0A

Rhodes

Rx Only

Lot

EXP

NO VARNISH

345 mm

441 mm

(b) (4)

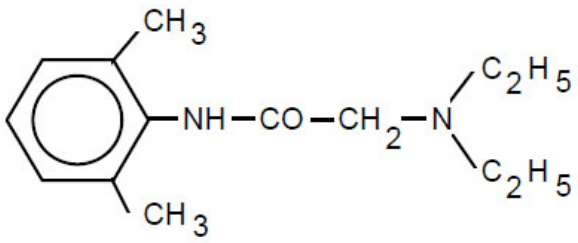
Lidocaine Patch 5%

Rx only

DESCRIPTION

Lidocaine patch 5% is comprised of an adhesive material containing 5% lidocaine, which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm x 14 cm.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol:water partition ratio of 43 at pH 7.4, and has the following structure:



Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: purified water, glycerin, sorbitol, polyacrylic acid, sodium carboxymethylcellulose, sodium polyacrylate, propylene glycol, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, edetate disodium, methylparaben, and propylparaben.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.

The penetration of lidocaine into intact skin after application of a lidocaine patch 5% is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

Pharmacokinetics

Absorption

The amount of lidocaine systemically absorbed from lidocaine patch 5% is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three lidocaine patches were applied over an area of 420 cm^2 of intact skin on the back of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The results are summarized in Table 1.

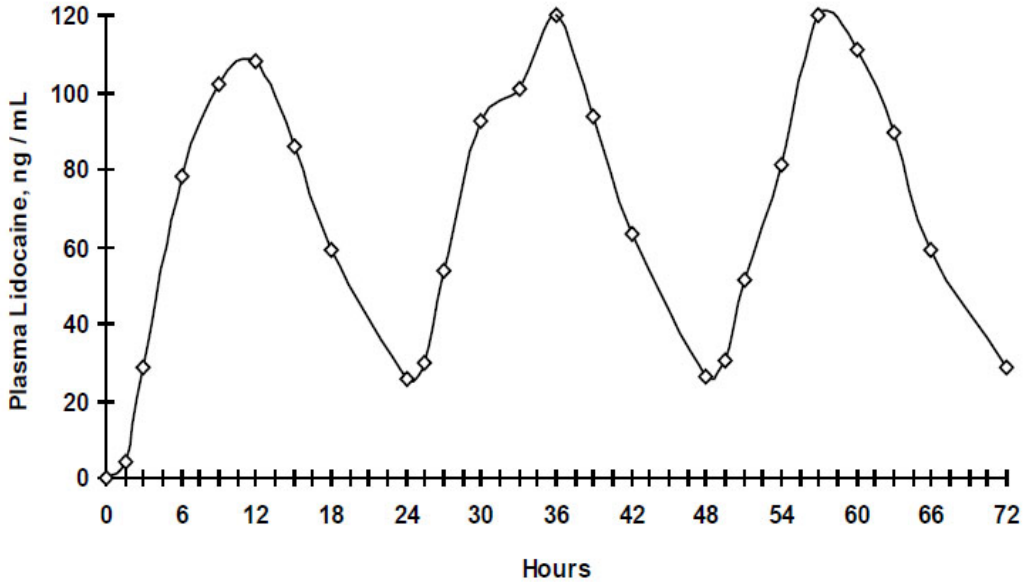
Table 1
Absorption of lidocaine from Lidocaine Patch 5%
Normal volunteers (n=15, 12-hour wearing time)

Lidocaine Patch 5%	Application Site	Area (cm^2)	Dose Absorbed (mg)	C_{max} (mcg/mL)	T_{max} (hr)
3 patches (2100 mg)	Back	420	64 ± 32	0.13 ± 0.06	11 hr

When lidocaine patch 5% is used according to the recommended dosing instructions, only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 mcg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for three days, indicated that the lidocaine concentration does not increase with daily use. The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1.

Figure 1

Mean lidocaine blood concentrations after three consecutive daily applications of three lidocaine patches simultaneously for 12 hours per day in healthy volunteers (n = 15).



Distribution

When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.6 SD, n = 15). At concentrations produced by application of lidocaine patch 5%, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 mcg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.

Metabolism

It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A

minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats. The blood concentration of this metabolite is negligible following application of lidocaine patch 5%. Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.

Excretion

Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 SD, n = 15).

CLINICAL STUDIES

Single-dose treatment with lidocaine patch 5% was compared to treatment with vehicle patch (without lidocaine), and to no treatment (observation only) in a double-blind, crossover clinical trial with 35 post-herpetic neuralgia patients. Pain intensity and pain relief scores were evaluated periodically for 12 hours. Lidocaine patch 5% performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours.

Multiple-dose, two-week treatment with lidocaine patch 5%, was compared to vehicle patch (without lidocaine) in a double-blind, crossover clinical trial of withdrawal-type design conducted in 32 patients, who were considered as responders to the open-label use of lidocaine patch 5% prior to the study. The constant type of pain was evaluated but not the pain induced by sensory stimuli (dysesthesia). Statistically significant differences favoring lidocaine patch 5% were observed in terms of time to exit from the trial (14 versus 3.8 days at p-value <0.001), daily average pain relief, and patient's preference of treatment. About half of the patients also took oral medication commonly used in the treatment of post-herpetic neuralgia. The extent of use of concomitant medication was similar in the two treatment groups.

INDICATIONS AND USAGE

Lidocaine patch 5% is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to **intact skin**.

CONTRAINDICATIONS

Lidocaine patch 5% is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

WARNINGS

Risk of Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert

more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue lidocaine patch 5% and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Accidental Exposure in Children

Even a *used* lidocaine patch 5% contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used lidocaine patch 5%, although the risk with this formulation has not been evaluated. It is important for patients **to store and dispose of lidocaine patch 5% out of the reach of children, pets, and others** (see HANDLING AND DISPOSAL).

Excessive Dosing

Excessive dosing by applying lidocaine patch 5% to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Systemic Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 mcg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of lidocaine patch 5%, the average peak blood concentration is about 0.13 mcg/mL, but concentrations higher than 0.25 mcg/mL have been observed in some individuals.

PRECAUTIONS

General

Hepatic Disease
Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.

Allergic Reactions
Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, lidocaine patch 5% should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Non-intact Skin
Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. Lidocaine patch 5% is only recommended for use on intact skin.

External Heat Sources
Placement of external heat sources, such as heating pads or electric blankets, over lidocaine patch 5% is not recommended as this has not been evaluated and may increase plasma lidocaine levels.

Eye Exposure
The contact of lidocaine patch 5% with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Information for Patients

Methemoglobinemia

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to stop use and seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

Drug Interactions

Antiarrhythmic Drugs

Lidocaine patch 5% should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Local Anesthetics

When lidocaine patch 5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Drugs That May Cause Methemoglobinemia When Used with Lidocaine Patch 5%

Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

Examples of Drugs Associated with Methemoglobinemia:

Class	Examples
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	Phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A minor metabolite, 2,6-xylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of lidocaine patch 5%.

Mutagenesis

Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test.

Impairment of Fertility

The effect of lidocaine patch 5% on fertility has not been studied.

Pregnancy

Teratogenic Effects
Pregnancy Category B.

Lidocaine patch 5% has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lidocaine patch 5% should be used during pregnancy only if clearly needed.

Labor and Delivery

Lidocaine patch 5% has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should lidocaine patch 5% be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Nursing Mothers

Lidocaine patch 5% has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk:plasma ratio of lidocaine is 0.4. Caution should be exercised when lidocaine patch 5% is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Application Site Reactions

During or immediately after treatment with lidocaine patch 5%, the skin at the site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Allergic Reactions

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Other Adverse Events

Due to the nature and limitation of spontaneous reports in postmarketing surveillance, causality has not been established for additional reported adverse events including:

Asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia, lightheadedness, metallic taste, nausea, nervousness, pain exacerbated, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.

Systemic (Dose-Related) Reactions

Systemic adverse reactions following appropriate use of lidocaine patch 5% are unlikely, due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (lightheadedness, nervousness, apprehension, euphoria,

confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold, or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension, and cardiovascular collapse leading to arrest.

OVERDOSAGE

Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS, Systemic Reactions), drug blood concentration should be checked. The management of overdose includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine.

In the absence of massive topical overdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects, or overdosage from other sources of lidocaine or other local anesthetics.

The oral LD_{50} of lidocaine HCl is 459 (346 to 773) mg/kg (as the salt) in non-fasted female rats and 214 (159 to 324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg, respectively, in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species.

DOSAGE AND ADMINISTRATION

Apply lidocaine patch 5% to intact skin to cover the most painful area. Apply the prescribed number of patches (maximum of 3), only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner (see HANDLING AND DISPOSAL). Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides.

When lidocaine patch 5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Lidocaine patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming, or showering.

HANDLING AND DISPOSAL

Hands should be washed after the handling of lidocaine patch 5%, and eye contact with lidocaine patch 5% should be avoided. Do not store patch outside the sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them. Lidocaine patch 5% should be kept out of the reach of children.

HOW SUPPLIED

Lidocaine patch 5% is available as the following:
Carton of 30 patches……. NDC 42858-118-30
(packaged in individual child-resistant envelopes)

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

For more information, call Rhodes Pharmaceuticals L.P. at 1-888-827-0616.
Marketed by:
Rhodes Pharmaceuticals L.P.
Coventry, RI 02816, USA

Manufactured by:
Altergon Italia Srl
Zona Industriale ASI, Morra de Sanctis
Avellino, 83040, Italy

303194-0A

Revised 01/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

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	3/16/2020
ANDA Number(s)	209190
Review Number	3
Applicant Name	Rhodes Pharmaceuticals L.P.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Lidocaine Patch 5%
Proposed Proprietary Name	NA
Submission Received Date	2/27/2020
Primary Labeling Reviewer	Rita Lindie
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments
☒ ACCEPTABLE – Include Post Approval Comments
☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

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

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

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

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

1. GENERAL COMMENTS
   Comment

2. CONTAINER LABEL
   a. Comment
   b. Comment

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

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

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

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

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

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

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

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

1.3 POST APPROVAL REVISIONS

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

PRESCRIBING INFORMATION
Remove the "Pregnancy Category B" per the Pregnancy and Lactation Labeling Rule (79 FR 72064).

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

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

Reviewer Comments:

Labeling was found to be acceptable in C2 review (1/23/2017 submission). Applicant submitted the following amendment

Rhodes Pharmaceuticals L.P. (Rhodes) is herein submitting a Labeling Amendment to the pending application to update the proposed product labeling to align with changes to the RLD. These changes are being made in accordance with 21 CFR 314.60.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments: Container and carton labeling were found to be acceptable in C2 review. Post approval comment from C2 (add the NDC number to the top third portion of the principal display panel per 21 CFR 207.35(b)(3) is no longer applicable per regulations.

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:

Click here to enter text.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review SLC to add language for Methemoglobinemia associated with the use of local anesthetics.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain.

(b) (4)

[redacted]

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

3.2 MODEL LABELING

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** (*If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)* **NDA# /Supplement# (S-000 if original):** 020612/S-014 **Supplement Approval Date:** 11/2/2018 **Proprietary Name:** Lidoderm® **Established Name:** lidocaine patch **Description of Supplement:** This supplemental new drug application provides for revisions to the labeling for LIDODERM consistent with our May 21, 2018, Safety Labeling Change Notification letter.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

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

Reviewer Comments: Applicant revised labeling to be in accordance with RLD, NDA 020612/S-014 approved 11/2/2018. Changes are acceptable.

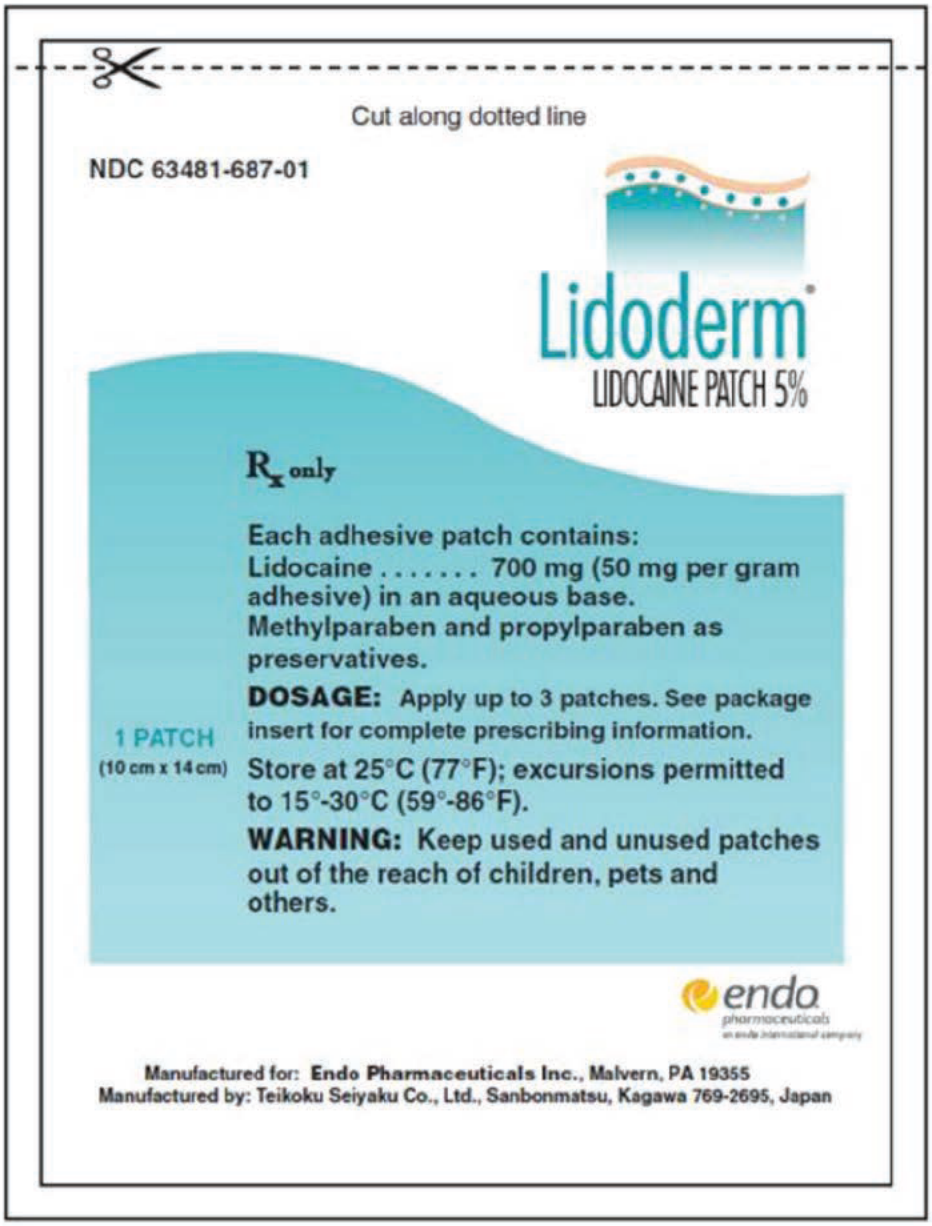
Post-approval comments (can be send out on 1st labeling revision if still applicable).

PRESCRIBING INFORMATION

Remove the "Pregnancy Category B" per the Pregnancy and Lactation Labeling Rule (79 FR 72064).

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS S-012 approval letter]



DIRECTIONS FOR USE

Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.

Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over LIDODERM patches is not recommended.

LIDODERM may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

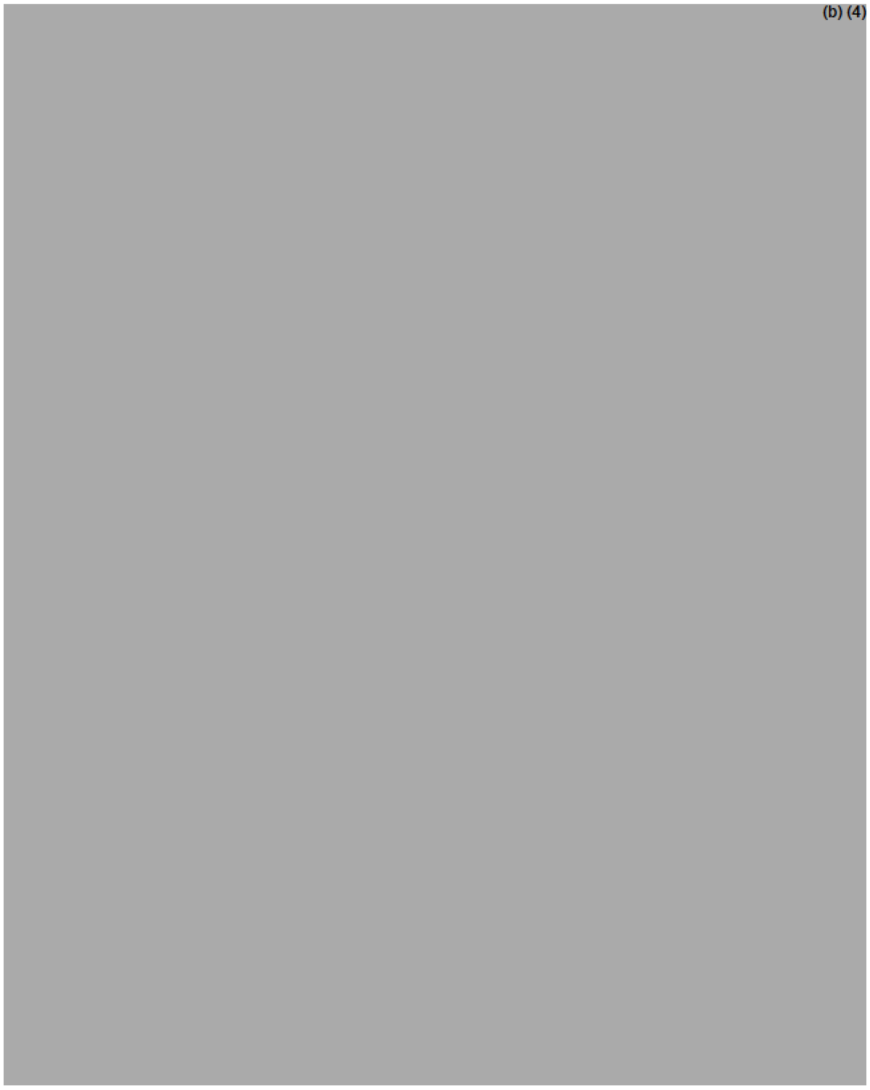
[redacted]

LOT:

EXP:

211374

1 Page has been withheld in full as b4 draft labeling immediately following this page



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 3/16/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	**Date**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
Currently Official	No		Click here to enter text.	Click here to enter text.
Not Yet Official	Click here to enter text.	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/16/2020.

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

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

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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

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

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
inactive ingredients: purified water, glycerin, sorbitol, polyacrylic acid, sodium carboxymethylcellulose, sodium polyacrylate, propylene glycol, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, disodium edetate, methylparaben and propylparaben.	inactive ingredients: purified water, glycerin, sorbitol, polyacrylic acid, sodium carboxymethylcellulose, sodium polyacrylate, propylene glycol, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, edetate disodium, methylparaben, and propylparaben.	No changes

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Lidocaine patch 5% is available as the following: **Carton of 30 patches…… NDC 42858-118-30** (packaged in individual child-resistant envelopes)	Lidocaine patch 5% is available as the following: **Carton of 30 patches…….. NDC 42858-118-30** (packaged in individual child-resistant envelopes)	No changes

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816 Manufactured by: Altergon Italia Srl, Morra de Sanctis Avellino 83040, Italy	Marketed by: Rhodes Pharmaceuticals L.P. Coventry, RI 02816, USA Manufactured by: Altergon Italia Srl Zona Industriale ASI, Morra de Sanctis Avellino, 83040, Italy	No changes

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

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

Refer to the Consult Screening flow chart to determine any necessary consults.

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

Reviewer Comments:

From CMC review finalized 3/3/2020

LABELING

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

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

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

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

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

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

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

If "No," explain.

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

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

ANDA Strength	Length (mm)	Imprint Code

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

None

List of Deficiencies:

N/A

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (patch)	Final	1 patch	1/23/2017	Satisfactory
Patch envelope	Final	1 envelope containing 1 patch	1/23/2017	Satisfactory
Carton	Final	30 patches (1 patch per envelope)	1/23/2017	Satisfactory
(Other – specify)	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	1/2019	2/27/2020	Satisfactory
Medication Guide	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements		Click here to enter text.	Click here to enter text.	Click here to enter text.

Rita Lindie

Digitally signed by Rita Lindie
Date: 3/16/2020 02:52:38PM
GUID: 53c570830001639fca7572eedfad43b0

Theresa Liu

Digitally signed by Theresa Liu
Date: 3/18/2020 11:56:07AM
GUID: 508da70a00028d58911de18a598cda6f

LABELING REVIEW

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

Date of This Review	2/27/2017
ANDA Number(s)	209190
Review Number	2
Applicant Name	Rhodes Pharmaceuticals L.P.
Established Name & Strength(s)	Lidocaine Patch 5%
Proposed Proprietary Name	NA
Submission Received Date	1/23/2017
Labeling Reviewer	Rita Lindie
Labeling Team Leader	Theresa Liu

Review Conclusion

☐ ACCEPTABLE – No Comments.

☒ ACCEPTABLE – Include Post Approval Comments

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

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

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

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

1. GENERAL COMMENTS
   Comment

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

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

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

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

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

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

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

1.3 POST APPROVAL REVISIONS

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

1. PATCH ENVELOPE
   Please add the NDC number to the top third portion of the principal display panel per 21 CFR 207.35(b)(3).

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

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

Reviewer Comments:

The below comments are from the labeling review C1 based on the submission dated 4/14/16.

1. GENERAL COMMENTS
   Include the country of origin on all your labeling pieces.

2. PATCH LABEL
   We note that final printed labeling (FPL) for the patch was not submitted for this application. Please ensure to include the established name and strength of the drug product, Lidocaine Patch 5%, on the patch when submitting FPL of the patch.

3. PATCH ENVELOPE
   a. Please ensure that the dotted line for cutting is only present on the top (as one single straight line), as opposed to along all four sides.
   b. We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Established Name) to improve its readability.
   c. Relocate "Rx Only" symbol and net quantity statement to the lower portion of principal display panel and remove the bold facetype.
   d. Revise "DOSAGE" to read as (b) (4)
   e. Add the following statement to appear in conjunction with the storage statement: "[see USP Controlled Room Temperature]".

4. CARTON LABELING
   See applicable patch envelope comments.

5. PRESCRIBING INFORMATION
   Please replace the abbreviation (b) (4) with "mcg" for clarity.

6. STRUCTURED PRODUCT LABELING (SPL)
   Revise the list of the inactive ingredients to reflect the list of the inactive ingredients in your package insert and consistent with your submission.

Applicant responded to all of the above comments. Per applicant, "please note that the dotted line for cutting will only be present on the top as one single straight line per FDA Easily Correctable Deficiency comment, Labeling: (3) (a) Patch Envelope. The light dotted lines, shown on the label, are for die line purposes to show the layout of the envelope heat seal to the back panel."

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.

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

Comments to applicant:

- Please add the NDC number to the top third portion of the principal display panel per 21 CFR 207.35(b)(3).

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:

NA to enter text.

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):** 020612/S-012 **Supplement Approval Date:** 1/7/2015 **Proprietary Name:** Lidoderm® **Established Name:** lidocaine patch **Description of Supplement:** This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, provides for the addition of the statements "Lidoderm may not stick if it is wet. Avoid contact with water such as bathing, swimming or showering." to the DOSAGE AND ADMINISTRATION section of the Package Insert, Overwrap Envelope, and Carton labeling.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** NA to enter text. **Supplement Approval Date:** NA to enter text. **Proprietary Name:** NA to enter text. **Established Name:** NA to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** NA to enter text.
☐ **OTHER (Describe):** NA to enter text.

Reviewer Assessment:

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

Reviewer Comments: Acceptable

NA to enter text.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS S-012 approval letter]

Cut along dotted line

NDC 63481-687-01

R_x only

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.

DOSAGE: Apply up to 3 patches. See package insert for complete prescribing information.

1 PATCH
(10 cm x 14 cm)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Keep used and unused patches out of the reach of children, pets and others.

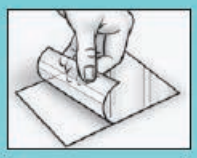
endo pharmaceuticals
an endo international company

Manufactured for: **Endo Pharmaceuticals Inc.**, Malvern, PA 19355
Manufactured by: Teikoku Seiyaku Co., Ltd., Sanbonmatsu, Kagawa 769-2695, Japan

DIRECTIONS FOR USE

Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.



Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over LIDODERM patches is not recommended.

LIDODERM may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

3 63481-687-017

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

211374

[redacted]

LOT:

EXP:

(b) (4)

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	3/8/2017	No	NA to enter text.	NA to enter text.
PF	3/1/2017	No	NA to enter text.	NA to enter text.

Reviewer Comments:

NA to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/1/2017.

Table 3 provides Orange Book patents for the Model Labeling NDA 020612 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 to enter text.						

Reviewer Assessment:

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

Reviewer Comments:

NA to enter text.

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

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

Reviewer Assessment:

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

Reviewer Comments:

NA to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: purified water, sorbitol, glycerin, polyacrylic acid, sodium carboxymethylcellulose, propylene glycol, sodium polyacrylate, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, disodium edetate, methylparaben and propylparaben.	Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: purified water, glycerin, sorbitol, polyacrylic acid, sodium carboxymethylcellulose, sodium polyacrylate, propylene glycol, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, disodium edetate, methylparaben and propylparaben.	No changes

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Lidocaine patch 5% is available as the following: Carton of 30 patches…… …… NDC 42858-118-30 (packaged in individual child-resistant envelopes)	Lidocaine patch 5% is available as the following: Carton of 30 patches…… … NDC 42858-118-30 (packaged in individual child-resistant envelopes)	No changes

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816	Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816 Manufactured by: Altergon Italia Srl, Morra de Sanctis Avellino 83040, Italy	Updated to include "manufactured by" information as requested by Agency.

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:

NA to enter text.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (patch)	Final	1 patch	1/23/2017	Satisfactory
Patch envelope	Final	1 envelope containing 1 patch	1/23/2017	Satisfactory
Blister	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
Carton	Final	30 patches (1 patch per envelope)	1/23/2017	Satisfactory

(Other – specify)	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	1/2017	1/23/2017	Satisfactory
Medication Guide	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
Patient Information	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
SPL Data Elements		1/2017	1/23/2017	Satisfactory

Theresa Liu

Digitally signed by Theresa Liu
Date: 3/02/2017 10:33:58AM
GUID: 508da70a00028d58911de18a598cda6f

Rita Lindie

Digitally signed by Rita Lindie
Date: 3/01/2017 11:16:48AM
GUID: 53c570830001639fca7572eedfad43b0

LABELING REVIEW

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

Date of This Review	1/4/2017
ANDA Number(s)	209190
Review Number	1
Applicant Name	Rhodes Pharmaceuticals L.P.
Established Name & Strength(s)	Lidocaine Patch 5%
Proposed Proprietary Name	NA
Submission Received Date	4/14/2016
Labeling Reviewer	Rita Lindie
Labeling Team Leader	Theresa Liu

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

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

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

☐ On Policy Alert List

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1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on January 5, 2017 based on your submission dated April 14, 2016:

1. GENERAL COMMENTS
   Include the country of origin on all your labeling pieces.

2. PATCH LABEL
   We note that final printed labeling (FPL) for the patch was not submitted for this application. Please ensure to include the established name and strength of the drug product, Lidocaine Patch 5%, on the patch when submitting FPL of the patch.

3. PATCH ENVELOPE
   a. Please ensure that the dotted line for cutting is only present on the top (as one single straight line), as opposed to along all four sides.
   b. We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Established Name) to improve its readability.
   c. Relocate "Rx Only" symbol and net quantity statement to the lower portion of principal display panel and remove the bold facetype.
   d. Revise "DOSAGE" to read a (b) (4)"
   e. Add the following statement to appear in conjunction with the storage statement: "[see USP Controlled Room Temperature]".

4. CARTON LABELING
   See applicable patch envelope comments.

5. PRESCRIBING INFORMATION
   Please replace the abbreviations (b) (4) with "mcg" for clarity.

6. STRUCTURED PRODUCT LABELING (SPL)
   Revise the list of the inactive ingredients to reflect the list of the inactive ingredients in your package insert and consistent with your submission.

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

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

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

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

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

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

1.3 POST APPROVAL REVISIONS

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

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

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

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if original):** 020612/S-012 **Supplement Approval Date:** 1/7/2015 **Proprietary Name:** Lidoderm® **Established Name:** lidocaine patch **Description of Supplement:** This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, provides for the addition of the statements "Lidoderm may not stick if it is wet. Avoid contact with water such as bathing, swimming or showering." to the DOSAGE AND ADMINISTRATION section of the Package Insert, Overwrap Envelope, and Carton labeling.

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

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: DARRTS S-012 approval letter)

Cut along dotted line

NDC 63481-687-01

R_x only

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.

DOSAGE: Apply up to 3 patches. See package insert for complete prescribing information.

1 PATCH
(10 cm x 14 cm)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Keep used and unused patches out of the reach of children, pets and others.

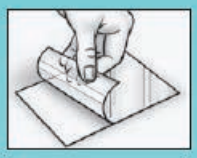
endo pharmaceuticals
an endo international company

Manufactured for: **Endo Pharmaceuticals Inc.**, Malvern, PA 19355
Manufactured by: Teikoku Seiyaku Co., Ltd., Sanbonmatsu, Kagawa 769-2695, Japan

DIRECTIONS FOR USE

Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.



Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over LIDODERM patches is not recommended.

LIDODERM may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

3 63481-687-01 7

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

211374

[redacted]

LOT:

EXP:

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	1/6/2017	NO	NA to enter text.	NA to enter text.
PF	1/5/2017	NO	NA to enter text.	NA to enter text.

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/5/2017.

Table 3 provides Orange Book patents for the Model Labeling (NDA 020612) 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 to enter text.						

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

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

2.5 MANUFACTURING FACILITY

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

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
3.2.P.3 Altergon Italia S.r.l. (Altergon), Zona Industriale A.S.L. Morra De Sanctis Avellino 83040 Ital (b) (4)	Container (envelope) Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816 Carton Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816	Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816

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? **NO**

Reviewer Comments:
Comments to applicant:
-Please replace the abbreviations "µg" with "mcg" for clarity.
- Include the country of origin on all your labeling pieces.

3.1.1.1 RX: DESCRIPTION

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

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

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
inactive ingredients: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, Dsorbitol, tartaric acid, and urea.	inactive ingredients: purified water, sorbitol, glycerin, polyacrylic acid, sodium carboxymethylcellulose, propylene glycol, sodium polyacrylate, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, disodium edetate, methylparaben and propylparaben.

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.) **YES**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO (See comment under Section 4)**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments: Acceptable
NA to enter text.

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	LIDODERM (lidocaine patch 5%) is available as the following: Carton of 30 patches, packaged into individual child-resistant envelopes NDC 63481-687-06 Store at 25°C (77°F); excursions permitted to 15o-30oC (59o-86oF). [See USP Controlled Room Temperature].
ANDA Labeling	Lidocaine patch 5% is available as the following: Carton of 30 patches…… …….NDC 42858-118-30 (packaged in individual child-resistant envelopes) Store at 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: Acceptable

3.1.2 RX: MEDICATION GUIDE

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

Reviewer Assessment:

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

Reviewer Comments:
NA to enter text.

3.1.3 RX: OTHER PATIENT LABELING

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

Reviewer Assessment:

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

Reviewer Comments:
NA to enter text.

3.1.4 RX: CONTAINER LABEL

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

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

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **NO**
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? **NO**
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? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**
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:
Comments to applicant:
-We note that final printed labeling (FPL) for the patch was not submitted for this application. Please ensure to include the established name and strength of the drug product, Lidocaine Patch 5%, on the patch when submitting FPL of the patch.
- Please ensure that the dotted line for cutting is only present on the top (as one single straight line), as opposed to along all four sides.
-We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Established Name) to improve its readability.
-Relocate "Rx Only" symbol and net quantity statement to the lower portion of principal display panel and remove the bold facetype.
-Revise "DOSAGE" to read as [redacted] (b) (4)
- Add the following statement to appear in conjunction with the storage statement: "[see USP Controlled Room Temperature]".
-Include the country of origin.

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

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

Reviewer Assessment:

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

Reviewer Comments:
NA to enter text.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable (other than Pharmacy Bulk Package)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

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

Reviewer Comments:
NA to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

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

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Is there a prominent, boxed declaration reading “Pharmacy Bulk Package – Not for Direct Infusion” on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:
NA to enter text.

3.1.5 RX: UNIT DOSE BLISTER LABEL

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

Reviewer Assessment:

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

Reviewer Comments:

NA to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

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

Reviewer Assessment:

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

Reviewer Comments:
Comments to applicant:
-See container label comments.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the established name for this ANDA acceptable? **NA**
Is title case used in expressing the established name? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **NA**
Is the following information properly displayed?
- Pharmacological category: **NA**
- Net quantity statement: **NA**
- Route(s) of administration (other than oral): **NA**
- Warnings (if any) or cautionary statements (if any): **NA**
- NDC: **NA**
- Bar code per 21 CFR 201.25(c)(2): **NA**

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

Reviewer Comments:
NA to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

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

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

Reviewer Assessment:

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

Reviewer Comments:
NA to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

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

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	**Description of Finished Product** (Source: NA to enter text.) NA to enter text. **Package Configurations** (Source: NA to enter text.) NA to enter text. **Storage Conditions** (Source: NA to enter text.) NA to enter text.
ANDA	**Description of Finished Product** (Source: NA to enter text.) NA to enter text. **Package Configurations** (Source: NA to enter text.) NA to enter text. **Storage Conditions** (Source: NA to enter text.) NA to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **NA**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **NA**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage statement acceptable as compared to the Model Labeling? **NA**
Is the storage statement acceptable as compared to USP? **NA**

Reviewer Comments:
NA to enter text.

3.2.2 OTC: PATIENT LABELING

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

Reviewer Assessment:

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

Reviewer Comments:
NA to enter text.

3.3 CONTAINER/CLOSURE

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

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **YES**
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 color? **NA to enter text.**
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:
From 3.2.P.7 QOS:

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

3.4 CALCULATIONS FOR CONTENTS IN LABELING

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

We verified the calculation on the following content.

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

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

Reviewer Assessment:

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

Reviewer Comments:
NA to enter text.

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

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

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

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? **NO**

Reviewer Comments:
Comments to applicant:
-Revise the list of the inactive ingredients to reflect the list of the inactive ingredients in your package insert and consistent with your submission.

4. COMMENTS FOR CHEMISTRY REVIEWER

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

(b) (4)

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:

6. SPECIAL CONSIDERATIONS

NA to enter text.

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 (Patch envelope)	Draft	1 envelope containing 1 patch	4/14/2016	Revise
Blister	NA to enter text.	NA to enter text.	NA to enter text.	NA to enter text.
Carton	Draft	30 patches (1 patch per envelope)	4/14/2016	Revise
(Other – Patch)	NA to enter text.	NA to enter text.	NA to enter text.	NA to enter text.
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	3/2016	4/14/2016	Satisfactory
Medication Guide	NA to enter text.	NA to enter text.	NA to enter text.	NA to enter text.
Patient Information	NA to enter text.	NA to enter text.	NA to enter text.	NA to enter text.
SPL Data Elements	NA to enter text.	3/2016	4/14/2016	Revise

Theresa Liu

Digitally signed by Theresa Liu
Date: 1/09/2017 09:18:02AM
GUID: 508da70a00028d58911de18a598cda6f

Rita Lindie

Digitally signed by Rita Lindie
Date: 1/09/2017 07:40:32AM
GUID: 53c570830001639fca7572eedfad43b0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

MEDICAL REVIEW(s)

Clinical Review of Comparative (Threshold) Analyses for Drug-Device Combination Products

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA#	209190
Drug Product	Lidocaine Patch
Strength(s)	5%
ANDA Applicant	Rhodes Pharmaceuticals LP
Reference Listed Drug (RLD)	Lidoderm (lidocaine) Patch, 5%
RLD#	020612
RLD Approval Date	3/19/1999
RLD Sponsor	Teikoku Pharma USA, Inc.
Primary Reviewer	Sunny Tse, PhD Clinical Reviewer, DCR/OB/OGD
Secondary Reviewer	Ying Fan, PhD Team Leader, ANDA Team, DCR/OB/OGD
Submission Date	4/14/2016
Materials Reviewed	• Draft Guidance "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (01/2017) • RLD labeling dated 1/2019 • Proposed generic product (ANDA) labeling dated 1/2019 • Test product and RLD samples provided by the Applicant: 9/4/2019
Date of Review	10/23/2019
GDUFA Goal Date	3/29/2020
Comparative Threshold Analyses Conclusion	☐ No Design Differences - Acceptable ☒ Minor Design Differences ☒ Acceptable ☐ Not acceptable ☐ Other Design Differences ☐ Acceptable ☐ Not acceptable

Deficiency Classification	☐ Major ☐ Minor ☒ **N/A (Review is Adequate)** ☐Comments to the Office of Pharmaceutical Quality (OPQ) ☐Comments to the Division of Labeling Review (DLR)

1 INTRODUCTION AND BACKGROUND

1.1 Summary of Drug Product Information Pertinent to Review

This is a comparative analysis of Rhodes Pharmaceuticals LP's ("Applicant") proposed generic Lidocaine Patch (5%) submitted under ANDA 209190 and the Reference Listed Drug (RLD), Lidoderm (lidocaine) Patch, 5%. The RLD was approved under NDA 020612 for relief of pain associated with post-herpetic neuralgia. The RLD is intended for administration by the user . The proposed and RLD drug products are delivered to the user via patch containing Lidocaine, (5%) and therefore, it is considered a complex drug-device combination product. There are currently 2 generic versions of the Lidocaine Patch (ANDAs 200675 and 202346).

This review evaluates the delivery device constituent part of the combination product intended to administer the drug product and any associated product labeling and packaging. This review focuses on the analysis of the user interface[1] for the drug-device combination product comparing the proposed generic and the RLD.

1.2 Other Relevant Information

All comparative threshold analyses reviews that have been completed for the proposed generic product (submitted by other applicants under separate ANDAs) have been reviewed. There are no pre-ANDA meeting packages or controlled correspondences for this drug product, referring to NDA 020612 as an RLD, that relate to drug-device design evaluation or comparative threshold analyses review.

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW AND DISCUSSION

DCR conducted a comparative analysis of the user interface of the proposed generic combination product and its RLD, Lidocaine Patch (NDA 020612).

2.1 Labeling Comparison: RLD vs. Proposed Generic Product

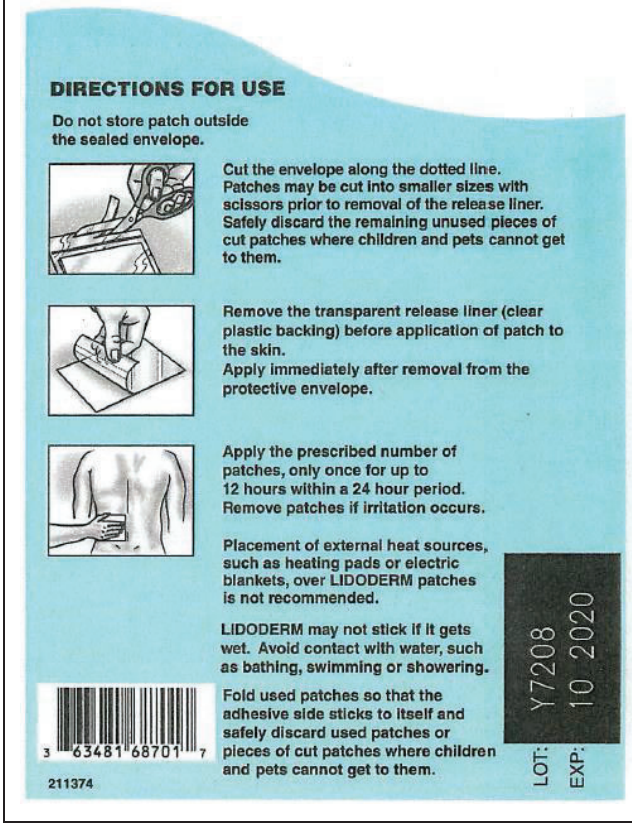
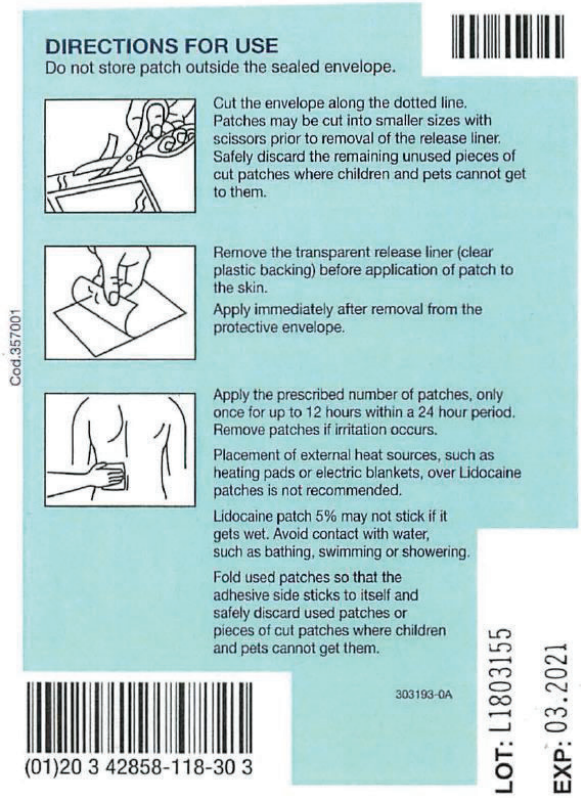
Side-by-side, line-by-line labeling comparison of the *Directions For Use* was conducted between the RLD and the proposed generic product. Except for the delivery device constituent part labeling, the review of the remainder of the label is deferred to the Division of Labeling Review (DLR). The RLD label was originally approved on 3/19/1999. The most current RLD label was revised 1/2019.[2] The RLD labeling includes Prescribing Information (PI) and Directions for Use.

[1] User interface refers to all components of the combination product with which a user interacts.
[2] NDA 020612 Lidoderm (lidocaine) Patch, 5% Label, revised 1/2019.
https://elist.fda.gov/prpllr/public/spl/7d6d88ee-72e5-4fda-9966-2975a96d9465/7d6d88ee-72e5-4fda-9966-2975a96d9465.view

Table 1: **Labeling Comparison: RLD vs. Proposed Generic Product**

Delivery device constituent part labeling: RLD vs. Proposed Generic Product	**Yes/No/NA**
(1) Any difference in the **description/design**?	**No**
(2) Any difference in the **administration**?	**No**
(3) Any difference in the **illustration(s)/figure(s)**?	**Yes-Minor**
(4) Any differences in the end-user Directions for Use?	**Yes-Minor**

Table 2: Comparison of RLD and Proposed Generic Product Directions for Use

RLD	Proposed Generic Product
	

Reviewer's Comments: *There were acceptable minor design differences identified in the Directions for Use between the proposed generic product and RLD. Text in the Directions for Use is the same for the RLD and proposed generic products. The figures in the IFU are similar. However, RLD figures have shading, whereas the proposed generic product figures do not. This difference is minor and acceptable.*

Overall, the labeling comparison supports that the proposed generic product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the proposed generic product.

2.2 Comparative task analysis: RLD vs. Proposed Generic Product

DCR examined the dosing delivery tasks of the proposed generic product compared to the RLD.

Reviewer's Comments: *There were no design differences identified in the tasks of administering/using the proposed drug product compared to the RLD product. The steps for using the generic product are the same as the steps for using RLD.*

Overall, the task analysis comparison supports that the proposed generic product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the proposed generic product.

2.3 Physical comparison of the delivery device constituent part: RLD vs. Proposed Generic Product

DCR examined the delivery device constituent part of the RLD and proposed generic product using samples provided by the Applicant. Representative photos are presented in Table 3below.

Table 3: Comparison of Actual Samples – Photos of RLD and Proposed Generic Product

(b) (4)

Photos taken by Reviewer on 9/12/2019

Reviewer's Comments*: The brand name Lidoderm® is printed on the RLD patch, and the generic name, Lidocaine Patch 5%, is printed on the proposed generic product. This is an acceptable minor design difference.*

Overall, the physical comparison of the delivery device constituent part supports that the proposed generic product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the proposed generic product.

3 APPLICANT'S THRESHOLD ANALYSES

ANDA 209190 is a GDUFA I ANDA. Therefore, the applicant did not submit threshold analyses in current submission.

4 CONCLUSION

From a clinical safety perspective, there are acceptable minor design differences between the RLD and proposed drug delivery device. Therefore, DCR concludes this generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product and that the design differences for this combination device does not alter the safety or efficacy profile of this proposed ANDA product under the conditions of use as specified in the labeling. In summary, DCR finds the proposed drug delivery device user interface for the proposed generic Lidocaine Patch **acceptable.**

5 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative (threshold) analyses and has:

No comments at this time.

Sunny Tse

Digitally signed by Sunny Tse
Date: 10/23/2019 06:36:36PM
GUID: 508da6ff0002855c7da84880bd716ed2

Ying Fan

Digitally signed by Ying Fan
Date: 10/24/2019 08:22:10AM
GUID: 507d9e07000062a73c410afff19b793c

Clinical Review of Skin Irritation, Sensitization and Adhesion Studies

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

ANDA number	209190
Drug Product	Lidocaine Topical Patch, 5%
Strength(s)	5%
Applicant Name	Rhodes Pharmaceuticals L.P.
Treatment Indication	Relief of pain associated with post-herpetic neuralgia
Reference Listed Drug (RLD)	Lidoderm® (lidocaine) Topical Patch, 5%
Reference Standard (RS)	Lidoderm® (lidocaine) Topical Patch, 5%
NDA number for RLD	020612
RLD Applicant Name	Teikoku Pharma USA, Inc.
Original Submission Date	04/14/2016
Materials Reviewed	FDA Statistical review by Somesh Chattopadhyay, PhD completed on 06/06/2017 FDA Statistical Addendum by Stella Grosser, PhD completed on 06/15/2017 OSIS inspection report: 12/08/2016 Draft Product Specific Guidance for Lidocaine Patch, 5%, recommended in 12/2006; Revised 05/2007, 07/2014, 01/2016
Primary Reviewer	Sunny Tse, PhD Clinical Reviewer, ANDA Team
Secondary Reviewer	Carol Y. Kim, PharmD Acting Team Leader, ANDA Team
Tertiary Reviewer	Sarah Yim, MD Division Director
Date of Completion	06/19/2017
GDUFA DATE	07/02/2017

DCR Conclusion	The application is recommended for approval from Division of Clinical Review (DCR) perspective. The adhesion data from PK/adhesion study RP-LID-PK001 are acceptable. The skin irritation and sensitization study RP-LID-SSI had multiple discrepancies in datasets which made it difficult to have confidence in the study results. However overall, the minor differences in test formulation compared to the reference product were not expected to pose any greater safety concern for irritation or sensitization potentials of the test product; nor were differences in irritation or sensitization suggested in RP-LID-PK001. Therefore DCR concludes the totality of the information in the application supports approval. OSIS inspection finding for the application is acceptable.

Table of Contents

Clinical Review of Skin Irritation, Sensitization and Adhesion Studies for ANDA 209190

1 EXECUTIVE SUMMARY

1.1 Approval Recommendation

The Division of Clinical Review (DCR) recommends approval of this application, contingent on approval recommendations from the other disciplines on the review team. OSIS inspection finding is acceptable.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

This review focuses on two studies submitted to ensure that the skin irritation and sensitization potentials of the applicant's Lidocaine Topical Patch, 5% (test product) are no greater than those of the reference listed drug (RLD) Lidoderm Topical Patch, 5%, and that the test product adheres to the skin as well as the RLD over the intended duration of wear. Two studies are skin irritation and sensitization study (RP-LID-SSI) and pharmacokinetic/adhesion study (RP-LID-PK001). The pharmacokinetic data and formulation are deemed adequate by the Division of Bioequivalence II (DBII).

1.2.2 Comparative Irritation

The applicant conducted one combined skin irritation and sensitization study (RP-LID-SSI). Study RP-LID-SSI was a randomized, single-center, controlled, evaluator-blinded, repeat insult patch test study to evaluate the potential for skin irritation and sensitization of a test Lidocaine Patch, 5% compared to the reference Lidoderm® (Lidocaine Patch, 5%) the Reference Listed Drug (RLD), in 248 healthy adult subjects. Both treatments (1/4 patch of test and reference products) were placed simultaneously for a 2-3 day wear cycle per application over a total of 9 applications (21 days of Induction Phase), followed by a 12-14 day Rest Phase and subsequent 48-hr Challenge phase, followed by a 3-day observation and irritation evaluation. Dermal irritation was assessed 0.5, 24, 48, and 72 hours after patch removal during the Challenge Phase. No subjects participated in a re-challenge phase.

According to the FDA analysis, the study RP-LID-SSI (test product, n=182, reference, n=180) demonstrates that the irritation potential of the test product is non-inferior to the reference. Using the least available number of study population number available based on further exclusion of subjects due to inappropriate study design by the FDA statistical reviewer, the FDA's upper bound of the one-sided 95% confidence interval of the test mean-1.25 reference mean is -0.041, within the non-inferiority margin of $\leq$=0. However, the FDA statistical reviewer concluded that the study data are not reliable to ensure adequate interpretation of the study results. The primary clinical reviewer also agreed that data integrity is in question. As a result, FDA statisticians and DCR clinical reviewers had a meeting on June 8, 2017. At this meeting, DCR secondary and tertiary reviewers discussed the rationale for DCR recommending approval of this application based on a weight of evidence approach, supported by other information available within submission; i.e., the difference in formulation (see Section 2.7) is not expected to be associated

with a change in irritation or sensitization potential, and the observed safety profile has not raised unexpected concerns (see Section 2.5 below).

1.2.3 Comparative Sensitization

Of 227 subjects evaluated from the same irritation/sensitization study RP-LID-SSI, no patch had evidence of potential sensitization reaction to either the test or the reference product. Also refer to Section 1.2.2 above.

1.2.4 Comparative Adhesion

The adhesive properties of Rhodes Pharmaceuticals L.P.'s Lidocaine Topical Patch, 5% and the reference were assessed in the pharmacokinetic/adhesion study (RP-LID-PK001) which was consistent with the draft product specific guidance. Study RP-LID-PK001 was a randomized, open-label, two-period, crossover, single dose bioequivalence and patch adhesion study enrolling 48 subjects. During each period, each subject received a single 12 hour application of 3 test products or reference products. After a rest period of 7 days, each subject received a single 12 hour application of the other treatment arm. Consistent with the draft product specific guidance, patch adhesion for each patch was assessed during each period at 6 hours (± 30 min) following patch application and prior to patch removal.

According to the FDA's analyses of adhesion performance between test product and the reference, the adhesion data from study RP-LID-PK001 demonstrate non-inferiority of the test product compared to the reference using the current FDA statistical method (Test-Reference ≤ 0.15). The upper bound of one-sided 95% confidence interval of Test mean minus Reference mean is -0.4075, which is within non-inferiority margin of ≤ 0.15. The study outcome is the same using the traditional FDA method (Test-1.25 Reference ≤0).

1.2.5 Comparative Safety

In irritation and sensitization study RP-LID-SSI (n=248), 129 (52.0%) subjects reported at least one adverse event. Most adverse events were mild or moderate in intensity. Three subjects experienced serious adverse events unrelated to the study drug and discontinued the study. Three subjects reporting a serious adverse event (SAE) had asthmatic bronchitis and acute upper respiratory infectio (b) (6) myocardial infarctio (b) (6) and left side radiculopath (b) (6) One subjec (b) (6) had a papular rash on the back and abdomen prior to patch application for the challenge phase. No death was reported. The most frequently reported adverse events were application site pruritus (42.3%), headache (6.9%), application site pain (5.2%), and back pain (3.6%). Because the applicant collected application site reactions without specifying treatment arm, it was not possible to compare the incidence of application site adverse events between test and reference products.

In pharmacokinetic/skin adhesion study RP-LID-PK001 (n=48), 2 subjects who applied the test product had treatment emergent adverse events (TEAEs). Subjec (b) (6) reported transient dizziness. Subjec (b) (6) reported headache, nausea, and vomiting. No TEAEs were reported following administration of the reference. No subject discontinued the study due to an adverse event. There were no SAEs reported. This study showed no clinically significant difference in safety profiles between the test and reference products.

2 CLINICAL REVIEW

2.1 Introduction and Background

2.1.1 Summary of Drug Information

Reference Listed Drug	LIDODERM®
RLD Applicant Name	Teikoku Pharma USA, Inc.
RLD NDA Number	020612
Date of RLD Approval	03/19/1999
Current Label[1]	01/2015
Approved Indication	relief of pain associated with post-herpetic neuralgia
Recommended Dose/Administration	• Apply the prescribed number of patches (maximum of 3), only once for up to 12 hours within a 24 hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. • LIDODERM may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.
Application site	Apply LIDODERM to intact skin to cover the most painful area.
Boxed Warnings	None
Commonly reported Adverse Events	**Application Site Reactions:** blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours **Allergic Reactions:** Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria.
Contraindications	LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.
Prominent Warnings/ Precautions	**Accidental Exposure in Children** Even a used LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020612s012lbl.pdf

	with this formulation has not been evaluated. It is important for patients to store and dispose of LIDODERM out of the reach of children, pets and others. **Excessive Dosing** Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects. Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest. Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 μg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of LIDODERM, the average peak blood concentration is about 0.13 μg/mL, but concentrations higher than 0.25 μg/mL have been observed in some individuals.
Mechanism of Action	Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.
Absorption	When LIDODERM is used according to the recommended dosing instructions, only 3 ± 2% of the dose applied is expected to be absorbed.

2.1.2 Regulatory Background

2.1.2.1 Guidance on Drug Product

A draft product specific guidance for Lidocaine Topical Patch, 5% is available. Table 2.1 provides a brief overview of the draft product specific guidance recommendations.

Table 2.1: Drug Product Guidance

Draft Product Specific Guidance	Draft Guidance on Lidocaine[2]
Date Posted	Recommended 12/2006; Revised 05/2007, 07/2014, 10/2016
Recommended Studies	1. Fasting Bioequivalence (BE) Study 2. Adhesion Study 3. Skin Irritation and Sensitization Study
Fasting BE Study	**Design:** Single-dose, in vivo, using three topical patches **Subject population**: Normal healthy males and females, general population **Treatment dosing**: Apply three topical patches simultaneously over a 12-hour period **Pertinent additional comments**: • Use fewer patches, provided the plasma concentrations of lidocaine are measurable to adequately characterize the pharmacokinetic profile of lidocaine for bioequivalence (BE) assessment based on the 90% confidence interval criteria. • Include a 24-hour post-dose sampling time in the BE study. • In addition to pharmacokinetic data, report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. Analyze and include in the calculation the amount of adhesive residue from each patch left on the skin.
Adhesion Study	**Design**: Randomized, single-dose, two-treatment in vivo **Subject population**: Healthy males and females, general population **Treatment dosing**: Adhesion performance of the intact test and RLD patches must be formally evaluated and may be compared in the pharmacokinetic (PK) BE study or in a separate parallel or crossover adhesion study of single 12-hour patch applications of the active test product versus the RLD. **Pertinent additional comments**: • No patch reinforcement is allowed when the study is being used to establish adequate adhesion performance to support product approval. Adhesion scoring is to be performed at least daily, in this case just prior to removal at the end of a 12-hour application. For patches that completely detach, a score of 4 should be carried forward in the adhesion analysis for all remaining observations in the

[2] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm086293.pdf

	application period.
Skin Irritation and Sensitization Study	**Design**: Randomized, evaluator-blinded, in vivo within-subject repeat test **Strength:** 5% (administered as one-fourth of the test and one-fourth of the reference) **Subject population**: Healthy males and females, general population **Treatment dosing**: Induction Phase - During the induction phase, all test articles (i.e., one-fourth of test product, one-fourth of the RLD, one-fourth of the optional vehicle patch, and optional negative control) are to be applied simultaneously to each subject at different sites. The test articles to be used are as follows: 1. One-fourth of test product (the test product evaluated should be the actual patches to be marketed.) 2. One-fourth of the RLD 3. One-fourth of the optional vehicle patch (the optional vehicle patch should have all of the inactive ingredients and be identical to the test product in every manner except for the absence of lidocaine.) 4. Optional negative control (an example of the optional negative control is an occlusion type device with normal saline applied on a polyester pad within the device chamber.) Sequential patch applications are to be applied to the same skin sites every 48-72 hours and to have each of them remain in place for 48-72 hours, for a total of 21 days altogether. Rest period – no patch application for 14-17 days Challenge phase – a single 48-hour application of one-fourth of the test product, one-fourth of the RLD, one-fourth of the optional vehicle patch, and the optional negative control to a naïve site **Pertinent additional comments**: • Adhesion should be evaluated prior to patch removal throughout the entire study period to ensure adequate skin contact for maximal induction of irritation and sensitization. • Irritation evaluation: Induction phase – at the time of each patch change; Challenge phase – 30 minutes and at 24, 48, and 72 hours after challenge patch removal. • For subjects who experience irritation consistent with a combined score of ≥ 3, or who experience symptomatic intolerable irritation, the patch may be moved to a new site in order to complete the 21-day Induction Phase and continue with the sensitization part of the study. • If a patch completely detaches, it should be replaced within 24 hours and the subject should continue in the study. During the 21-day Induction Phase, if a patch is completely detached for more than 24

	hours (unless the patch was removed for an unacceptable degree of irritation), the subject should be excluded from both the irritation and sensitization analyses for that product. During the 48-hr Challenge Phase, if a patch is completely detached for more than 24 hours, the subject should be excluded from the sensitization analysis. • Due to safety concerns, it is not recommended to simultaneously apply two whole, active, Lidocaine Patch 5% patches on the same subject during the 21-day skin irritation and sensitization study. The optimum design of this study will depend on the design of the test product patch. Since the RLD has a matrix design that can be safely cut, one-fourth of the patch can be used for these studies. If the test product patch also has a design that can be cut to a smaller size, it should also be cut in one-fourth and one-fourth of the test product patch applied simultaneously with one-fourth of a RLD patch (to separate skin sites). It would not be acceptable to manufacture a separate batch of product in order to use a smaller patch in this study.

Guidance for Industry

On 6/1/2016, the FDA posted a draft guidance for industry entitled *Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs (June 2016)*[3] ("Adhesion Guidance"). This Adhesion Guidance provides updated recommendations for the design and conduct of adhesion studies. The Adhesion Guidance also includes updated statistical analysis method to evaluate adhesion performance.

2.1.2.2 Generic Product Development

The applicant did not submit controlled correspondences and protocol for this application.

2.1.2.3 Relevant Communications with Other Generic Applicants

Mercado searches yielded 25 results, none of which were relevant to the skin irritation, sensitization, and adhesion studies evaluated for this current application.

2.1.2.4 Other ANDA submissions for same or related product

ANDA	Applicant	Current Status	Status Date
200675	ACTAVIS LABORATORIES UT INC	Approved	8/23/2012
202346	MYLAN TECHNOLOGIES INC	Approved	8/7/2015
[redacted]			(b) (4)
203265	NOVEN PHARMACEUTICALS INC	Complete Response issued – Adequate DCR review	09/13/2016
[redacted]			(b) (4)

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf

ANDA	Applicant	Current Status	Status Date
205882	KREMERS URBAN MANUFACTURING INC	Pending - DCR recommended approval	10/26/2016
206463	AMNEAL PHARMACEUTICALS	Pending - DCR recommended approval	07/20/2016
[redacted]			(b) (4)

2.1.3 Other Relevant Information

none

2.2 Description of Clinical Data and Sources

The applicant conducted one combined skin irritation and sensitization study (RP-LID-SSI) and pharmacokinetic/skin adhesion study (RP-LID-PK001).

Table 2.2: Source of Clinical Data

Study #	RP-LID-SSI	RP-LID-PK001
Study Type	skin irritation and sensitization	pharmacokinetic/adhesion
CRO	Frontage Clinical Services Inc.	Frontage Clinical Services Inc.
Study Period	08/12/2013 to 12/16/2013	08/22/2013 to 09/18/2013
Study Center	Frontage Clinical Services Inc. 241 Main Street Hackensack, New Jersey 07601	Frontage Clinical Services Inc. 241 Main Street Hackensack, New Jersey 07601
Enrollment	248	48

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

ANDA Submission(s)	**04/14/2016 (eCTD Sequence 0000):** Original Submission **05/23/2016 (eCTD Sequence 0001):** Response to Information Request from Division of Filing Review – datasets **08/15/2016 (eCTD Sequence 0003):** Response to ECD from Statistics dated 08/30/2016 for irritation and sensitization study RP-LID-SSI – questions regarding skipped visits, patch adhesion, make-up patches **09/06/2016 (eCTD Sequence 0004):** Response to ECD from DCR dated 08/23/2016 for irritation and sensitization study RP-LID-SSI – questions

	regarding patch reinforcement and adverse events **09/29/2016 (eCTD Sequence 0005):** Response to ECD from DCR dated 09/16/2016 for irritation and sensitization study RP-LID-SSI – questions regarding irritation assessment, patch adhesion, and application site adverse events **10/21/2016 (eCTD Sequence 0006):** Response to ECD from Statistics dated 10/03/2016 for irritation and sensitization study RP-LID-SSI – questions regarding dataset discrepancies **12/09/2016 (eCTD Sequence 0007):** Response to ECD from Statistics dated 11/18/2016 for irritation and sensitization study RP-LID-SSI – issues regarding datasets and study procedure This ANDA is submitted in eCTD format and entirely electronic. The ANDA submission is archived at the following location: \\cdsesub1\evsprod\ANDA209190\209190.enx
FDA Statistical Review	ANDA 209190 Statistical Primary Review ("A209190_statistical.doc") by Somesh Chattopadhyay, PhD, Completed on 06/06/2017

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Study #	RP-LID-SSI	RP-LID-PK001
Office of Study Integrity and Surveillance	Establishment Inspection Report review submitted 12/08/2016. Please see section 2.6.1 for details.	Decline to Inspect Memo submitted 05/19/2016. Please see section 2.6.1 for details.
Blinding	Irritation and sensitization evaluator blinded	Evaluation of dermal reactions at the application sites was clinically assessed in a blinded fashion 30 minutes and 12 hours after patch removal
Randomization	site of patch application: one side of the infrascapular area of the back; 2-location (upper/lower) randomization	two treatment sequences (T-R, R-T)
Retention of Reserve Samples	n/a	Retention (reserve) samples of the reference and test formulation were selected and retained by the Principal Investigator (or designee) in a locked, secure pharmacy cabinet in compliance wit (b) (4) Standard Operating Procedures.

Reviewer's comments:

- *The irritation/sensitization evaluator was blinded for study RP-LID-SSI. The applicant's method of blinding is acceptable.*
- *Randomization is acceptable for both studies RP-LID-SSI and RP-LID-PK001.*
- *OSIS indicated the study data for study RP-LID-SSI were acceptable.*
- *OSIS declined to inspect study RP-LID-PK001 clinical site due to acceptable inspection history.*

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

Studies RP-LID-SSI and RP-LID-PK001 appear 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 for both studies.

2.3.4 Evaluation of Financial Disclosure

For studies RP-LID-SSI and RP-LID-PK001, a Form FDA 3454 (dated 03/04/2016) is submitted for all investigators. The applicant had no financial arrangements with the investigators to disclose.

2.4 Review of Skin Irritation, Sensitization, and Adhesion

2.4.1 General Approach to Review of Skin Irritation, Sensitization and Adhesion

Study RP-LID-SSI was reviewed to verify that test product is no more irritating and sensitizing than the reference. RP-LID-PK001 was reviewed to verify that the adhesion performance of the test product is no worse than that of the reference.

2.4.2 Detailed Review of Skin Irritation, Sensitization and Adhesion Studies

2.4.2.1 Skin Irritation and Sensitization Study (RP-LID-SSI)

Applicant's Study #:	RP-LID-SSI
Title	A Randomized, Controlled Study to Evaluate the Skin Irritation and Sensitization Potential of a Test Lidocaine 5% Topical Patch Compared to Lidoderm 5% Topical Patch Using a Repeat Insult Patch Test Design in Healthy Adults

Objectives	The primary objectives of this study were: • To evaluate the skin irritation induced by topical application of the test lidocaine 5% patch compared to Lidoderm 5% lidocaine patch following 21 days of exposure in healthy adult male and female subjects. • To evaluate the skin sensitization induced by topical application of the test lidocaine 5% patch compared to Lidoderm 5% lidocaine patch after a 21-day Induction Phase, followed by a 48-hour Challenge Phase in healthy adult male and female subjects. The secondary objective of this study was: • To assess the safety and tolerability of a test lidocaine 5% topical patch compared to Lidoderm 5% lidocaine patch in healthy adult male and female subjects.

2.4.2.1.1 Protocol Review

Protocol Version	Protocol Date	IRB Approval Date
1.0	07/25/2013	07/31/2013

Reviewer's comments:
The protocol was approved prior to study initiation (study period: 08/12/2013 to 12/16/2013).

2.4.2.1.2 Study Design

Overall Study Design
Study RP-LID-SSI was a two treatment, single site, multiple-application, evaluator-blinded, three-phase, randomized study in 248 healthy adults. Cumulative skin irritation and sensitization potentials of the test product were compared to reference by repetitive placement of each treatment to the same skin site. Both treatments (1/4 test product patch and 1/4 reference product) were placed simultaneously and replaced 3 times weekly at the study site for a total of 9 applications (21 days of Induction Phase). If patch adhesion was assessed as <50% adhered but not detached (more than half the system lifting off of the skin without falling off), the subject was scheduled for a make-up patch application. The skin irritation assessment for the patch adhered <50% was not included in the irritation analyses. Subjects who did not return for one visit to the study site during the Induction Phase were instructed to keep the patches in place. They were scheduled to receive a make-up patch application at the last visit during the Induction Phase. The make-up patches were removed 48 hours later and the patch sites were assessed. There was a 12-14-day rest phase. Then followed a subsequent 48-hr Challenge phase, with a 3-day observation and irritation evaluation. Dermal irritation was assessed 0.5, 24, 48, and 72 hours after patch removal during the Challenge Phase. There were 2 cohorts. The Cohort 1 treatment start date was 08/20/2013. The last Cohort 1 treatment exposure date was 09/26/2013. The Cohort 2 treatment start date was 11/05/2013. The last Cohort 2 treatment exposure date was 12/13/2013.

Table 2.3: Overall Study Design

Study/Protocol Number	RP-LID-SSI		
Subject Population	Healthy, adult subjects who met the inclusion/exclusion criteria for this study		
Blinding	This study was blinded to the study staff performing the irritation and sensitization assessments.		
Randomization	Application sites were designated as "upper" and "lower" on the randomization schedule, which pertained to the relative positioning of the test and reference study products to each other.		
Treatment arms	**Test**		**Reference**
Reinforced	Yes		Yes
Number of period/phase	**Induction**	**Rest**	**Challenge**
Duration	21 days	12-14 days	5 days
Dose administered	1/4 test patch 1/4 reference patch	none	1/4 test patch 1/4 reference patch
Dosing regimen	1/4 test patch 1/4 reference patch	none	1/4 test patch 1/4 reference patch
Number of applications	3 times/week applications; total of 9 for test and reference	none	1 for test and reference
Application site	Study patches were applied simultaneously to the same sites on one side of the infrascapular area of the back. Subjects returned to the study site at 48-hour intervals to have the 1/4 patches removed and replaced by study site personnel. 1/4 patches applied on Friday remained in place for 72 hours until Monday. 1/4 patches applied on Saturday remained in place for 72 hours until Tuesday.	none	The test and reference study patches were applied to naïve sites on the opposite side of the spine on Day 36 for 48 hours or until removal due to excessive local irritation. The respective site of application ("upper" or "lower") was the same as that used during the Induction Phase.
Adhesion assessment times	prior to removal of each 1/4 patch	none	prior to removal of each 1/4 patch
Irritation assessment times	following removal of each 1/4 patch and prior to 1/4 patch replacement	none	0.5, 24, 48, and 72 hours after 1/4 patch removal

Reviewer's comments:
The applicant's study design is different from the draft product specific guidance. The applicant allowed an additional "make-up" patch if patch adhesion was less than 50%. In addition, the applicant's Other Effects scale for skin reactions included one additional "no other observations", which is not present in the product specific guidance. For Other Effects scale, the applicant used continuous numerical scores of 0 to 6 whereas the drug specific guidance

recommends numeric equivalent scores of 0 to 3 only. The FDA statistical analyses relied on the FDA-recommended scale and study design for the analyses of irritation and sensitization.

Treatment Arms

Table 2.4: Treatment Arms (Study # RP-LID-SSI)

Treatment arms	Test	Reference
Product Name	Lidocaine Topical Patch, 5%	Lidoderm® (lidocaine) Topical Patch, 5%
Strength	5%	
Patch size	Length: 14 cm, Width: 10 cm (¼ patch of the test product was applied)	Length: 14 cm, Width: 10 cm (¼ patch of the reference product was applied)
Manufacturer	Altergon, Italia	(b) (4) for Endo Pharmaceuticals
Batch/Lot No.	L1304191	Y2282
Manufacture Date	04/2013	n/a
Expiration Date	n/a	10/2015
Dosage Form	topical patch	
Route of administration	topical	
Reinforced with tape	Yes	

Study Population Selection

This study enrolled male and female subjects at least 18 years old. See applicant's study report, Section 9.6 (pages 29-30 of 149) for the full list of the applicant's inclusion and exclusion criteria.

Reviewer's comments:

The applicant's inclusion/exclusion criteria incorporated all the inclusion and exclusion criteria from the draft product specific guidance. All of the applicant's additional inclusion and exclusion criteria are acceptable. A key applicant inclusion criterion was that a subject was to be free of any systemic or dermatologic disorder, which, in the opinion of the investigator, would interfere with the study results or increase the risk of adverse event. Two of these key applicant exclusion criteria were: Not willing to refrain from swimming or bathing such that the patch will be submerged for the duration of the study and not willing to refrain from excessive exercise or physical activity for the duration of the study.

Restrictions during the study	Subjects could not use systemic/topical analgesics (e.g. aspirin, Aleve, Motrin, Advil, Nuprin) for at least 72 hours prior to and during the study. Subjects could take occasional acetaminophen as needed for headache or other pain. Subjects could not use systemic/topical corticosteroids for at least 3 weeks prior to or during the study. Subjects could not use systemic/topical antihistamines for at least 72 hours prior to or during the study. Other over-the-counter or prescription medications were prohibited during the study, including during the Rest Phase, unless approved by the Sponsor and investigator on a case-by-case basis. Female subjects using hormonal

	contraceptives continued therapy during the study. Whereas bathing was allowed (low tub bath/frontal showers), the patched area was not to be soaked and was to be kept as dry as possible, per the instructions given to each subject.
Treatment compliance	All patches were applied and removed by clinical study staff. Records of patch applications and visit schedule compliance were recorded on the subjects' source documents and CRFs.

Reviewer comments

- *The restrictions on medication use during the study reflect the applicant's exclusion criteria and are acceptable. The RLD labeling recommended avoidance of patch contact with water, such as showering. The applicant's allowance of frontal showers was an acceptable compromise to maintain subject hygiene as the patch application site was on the back and the induction phase was 21 days.*
- *The applicant's measures to ensure treatment compliance are acceptable.*

Assessments
The applicant used the following scales and sensitization definition during study RP-LID-SSI:

Table 2.5: Dermal Response

Score	Description
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible, minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema with edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond application site

Table 2.6: Other Effects

Score	Description
0	no other observations
1	slightly glazed appearance
2	marked glazed appearance
3	glazing with peeling and cracking
4	glazing with fissures
5	film of dried serous exudates covering all or part of the patch site
6	small petechial erosions and/or scabs

Sensitization Definition
A skin sensitization reaction was defined as the development, at the site of re-exposure to the patch, of definite erythema combined with the presence of any of the following signs: papules, edema, vesicles, bullae, cracking, fissuring, crusting, peeling, or spread beyond the confines of patch application site. Such reactions were required to have a time course compatible with a sensitization reaction; that is, such a reaction occurring at the beginning of the Induction Phase was deemed a sign of prior sensitization, and reactions which markedly improved within a 72-96 hour timeframe were not characteristic of an allergic response, and were classified as an irritant response. Skin sensitization reactions most likely occur in the Challenge Phase, although they could occur later in the Induction Phase, and would have a time course characteristic of Type IV delayed hypersensitivity reactions.

Reviewer's comments:

- *The applicant's Dermal Response scale is the same as recommended by the draft product specific guidance.*
- *The applicant's Other Effects scale for skin reactions had an additional observation, "no other observations", which was not present in the product specific guidance. Also, the applicant's Other Effects scale numeric scoring was different than what is recommended in the product specific guidance. The FDA statistical reviewer followed the draft product specific guidance's numerical scale.*

- *The FDA statistician followed the draft product specific guidance sensitization criteria for the FDA analysis.*

Endpoints

Primary Endpoints	Dermal response scores and scores for other effects • Dermal response scores and scores for other effects collected during the Induction Phase to evaluate the skin irritation potential of the study product. • Dermal response scores and scores for other effects collected during the Challenge Phase to evaluate the skin sensitization potential of the study product. • The number of patches removed due to an unacceptable degree of irritation. • The number of days until sufficient irritation occurs to preclude patch application.

Reviewer's comments:
The applicant's primary endpoints are acceptable.

Statistical Analysis Plan
See applicant's study report, Section 9.10 (page 37) and FDA Statistical Review, Section 3.2.7.2 – 3.2.7.4 (pages 34 - 38) for details of the statistical analysis plan. The applicant's analysis populations definitions are provided below.

Applicant's Irritation Analysis Population
Irritation:
The applicant's irritation analysis population included all subjects who received test/reference products such that sequential test/reference product applications were not detached from the skin for longer than 24 hours during the 21-day Induction Phase (unless the patch was removed for an unacceptable degree of irritation). If a test/reference product detached and could not be replaced within 24 hours, or a subject did not know when a test/reference product detached, the subject's patch was excluded from the test/reference irritation analysis population.

Sensitization:
All subjects who received test/reference products (Challenge Phase) and who have completed the Induction Phase, wearing the test/reference products for the entire 21 days and completed the Rest Phase. Additionally the challenge test/reference products must be attached for 48 hours (unless the challenge test/reference product was removed due to a sensitization reaction) with the subject returning for evaluation at least 24 hours after removal of the challenge test/reference product.

Reviewer's comments:
The applicant's irritation analysis population definition is consistent with the draft product specific guidance per-protocol population for irritation.

The applicant's sensitization analysis population definition is different than the draft product specific guidance sensitization analysis population definition. The draft product specific guidance recommends the subject to return for at least one of the scheduled evaluations at 48

and 72 hours after removal of the challenge patch. However, the applicant's sensitization analysis population includes subjects who return for evaluation at least 24 hours after removal of the challenge patch. The FDA statistician used the definition specified in the drug specific guidance for the FDA analysis.

2.4.2.1.3 Study Subjects

Subject Disposition
Two hundred forty-eight (248) healthy adult subjects were entered into this study and received at least one application of patches. A total of 227 subjects completed the study.

Subjects Analyzed
Of the 248 subjects randomized into the study, 228 test subjects and 228 reference subjects were included in the applicant's irritation PP population and 227 test subjects and 227 reference subjects were included in the applicant's sensitization PP population.

Reviewer's comments:
The FDA clinical reviewer did not recommend any changes to the applicant's irritation and sensitization PP populations for the FDA analysis.[4]

Demographics
The demographics of the irritation and sensitization study RP-LID-SSI are as follows.

Table 2.7: Demographic and Baseline Characteristics for Irritation and Sensitization Study: Gender, Race and Age

		All Enrolled (N=248)
Gender	Female	184 (74.19%)
	Male	64 (25.81%)
Race	Asian	3 (1.21%)
	Black	135 (54.44%)
	White	110 (44.35%)
Age Group in Years	18-40	111 (44.76%)
	41-64	129 (52.02%)
	65-75	8 (3.23%)
Age in Years	Mean, SD	41.39, 12.22
	Min, Max	18, 69
	Q1, Median, Q3	33, 43, 49

Source: FDA Statistical Report Table 18

[4] http://panorama.fda.gov/document/preview?versionID=5775b58a0093c7eb4704e2b302f4bb00&ID=5775b58a0093c7ea3a9a373c525c3883

Reviewer's comments:
There was a higher percentage of females in the study. Enrolled subjects consist mainly of black and white subjects. The age range of subjects is consistent with the applicant's inclusion criteria of ≥ 18 years of age. These demographics are acceptable and have no impact on the study outcome because both test and reference patches were applied simultaneously to the same subject.

2.4.2.1.4 Results

Irritation Results
The applicant's irritation analysis results are as follows.

Table 2.8: Applicant Irritation Analysis Results (Study RP-LID-SSI)

Variable	Hypotheses	LSmean Test	LSmean Reference	Estimate of $\mu_A - 1.25*\mu_B$	One-Sided 95% Upper Confidence Bound
Mean Irritation Score ("dermal response" + "other effects" scores from induction phase assessments)	H_0: $\mu_A - 1.25*\mu_B \geq 0$ H_1: $\mu_A - 1.25*\mu_B < 0$	0.211	0.212	-0.001	-0.015

Source: Applicant Study Report Table 9

Because the applicant's study design is significantly different from the recommendation provided in the drug specific guidance for this product due to additional make-up patch use, FDA statistical reviewer performed 6 different study populations post-hoc to evaluate whether those protocol violations identified by the FDA statistical reviewer change the study outcome. FDA statistical reviewer identified multiple data inconsistencies in irritation scores from the original dataset to subsequent datasets in response to their ECD requests.

The 6 variants of the PP population considered for the FDA irritation analysis (PPPI1 – PPPI6) included adjustments which removed subjects due to a significant protocol deviations or violations. The definition for each study population and the summary results are listed below.

The patches excluded from PPPI1 are:

- A patch type that did not have all nine patch applications or did not have all nine irritation assessments for a subject.
- All patches from Subject (b) (6) This is based on the OSIS inspection report.

The patches excluded from PPPI2 are:

- All patches excluded from PPPI1.
- All patches from the subjects who skipped a visit during the induction phase.

The patches excluded from PPPI3 are:

- All patches excluded from PPPI1.
- All patches that were detached during the induction phase based on the patch detachment flag but not known to be replaced within 24 hours after detachment. The datasets submitted on December 9, 2016 were used for this determination.

The patches excluded from PPPI4 are:

- All patches excluded from PPPI3.
- All patches from the subjects who skipped a visit during the induction phase.

The patches excluded from PPPI5 are:

- All patches excluded from PPPI1.
- All patches that were detached during the induction phase based on the adhesion scores but not known to be replaced within 24 hours after detachment. The datasets submitted on December 9, 2016 were used for this determination.

The patches excluded from PPPI6 are:

- All patches excluded from PPPI5.
- All patches from the subjects who skipped a visit during the induction phase.

Table 2.9: Irritation Analysis Results (Study RP-LID-SSI)

	Applicant		FDA											
	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]
Irritation Analysis PP Population	Applicant's FIAP		PPPI1		PPPI2		PPPI3		PPPI4		PPPI5		PPPI5	
Variable	CII[3]		MIS[4]		MIS[4]		MIS[4]		MIS[4]		MIS[4]		MIS[4]	
Number of Patches	228	228	222	222	196	196	193	192	176	175	199	199	182	180
Mean	0.211	0.212	0.206	0.210	0.209	0.214	0.220	0.224	0.223	0.227	0.216	0.226	0.218	0.227
SD	0.354	0.344	0.323	0.345	0.341	0.354	0.336	0.350	0.345	0.360	0.333	0.354	0.341	0.362
Upper 95% UCB[5] for Test –Reference[6]	0.015													
Upper 95% UCB[5] for Test - 1.25*Reference[7]	-0.034		-0.038		-0.038		-0.039		-0.041		-0.039		-0.039	
Conclusion: Is Test Non-Inferior to Reference?	Yes		Yes		Yes		Yes		Yes		Yes		Yes	
Sensitization Analysis PP Population	Applicant's FSAP		PPPS1		PPPS2		PPPS3		PPPS4		PPPS5		PPPS5	
Number of Patches	225	225	217	215	191	189	187	186	170	169	192	193	175	174
Number of Sensitization	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[1]Test: Lidocaine 5% topical patch (Distributed by Rhodes Pharmaceuticals L.P. and manufactured by Altergon, Italia)
[2]Reference: Lidoderm® (lidocaine patch 5%) (manufactured by Teikoku Seiyaku Co., Ltd. for Endo Pharmaceuticals, Inc.)
[3]CII: Cumulative Irritancy Index defined by the applicant as the mean of the irritation scores (dermal response + other effects) during the induction phase. Applicant's other effects scale is different from FDA's.
[4]MIS: Mean irritation score is the mean of the 9 irritation scores (dermal response + other effects) during the induction phase.
[5]UCB=Upper Confidence Bound
[6]Applicant's non-inferiority criterion: 95% UCB for Test – Reference <0.11; [7]FDA's non-inferiority criterion: 95% UCB for Test – 1.25*Reference <0.
Source: FDA Statistical Report Table 74

Reviewer's comments:
The results of all six above-mentioned FDA irritation analyses demonstrate non-inferiority of the test product to the reference product. However, due to inconsistency in irritation scores reported in multiple datasets, DCR primary reviewer cannot make adequate conclusion of irritation assessment from the irritation and sensitization study RP-LID-SSI. Please see FDA statistical report for further details.

Sensitization Results

Table 2.10: Patches with Irritation Score ≥ 2 at 48 or 72 Hour Evaluation in Challenge Phase

Subject ID	Treatment*	Irritation Scores at Different Times after Challenge Phase Patch Removal				Max Irritation Score During Induction Phase	Applicant's Determination of Potential Sensitization in the Challenge Phase (Yes, No)	FDA Determination of Potential Sensitization (Yes, No) Based on Irritation Scores
		30 Mins	24 Hrs	48 Hrs	72 Hrs			
(b) (6)	A	1	2	2	1	2	No	No
	B	1	2	2	1	3	No	No

*: A=Test, B=Reference.
Source: FDA Statistical Report Table 60

Reviewer's comments:
No subjects demonstrated a sensitization response during this study. However, due to same reason as stated above, DCR primary reviewer cannot make adequate conclusion regarding sensitization potential. Please see FDA statistical report for further details.

2.4.2.2 Pharmacokinetic/Skin Adhesion Study (RP-LID-PK001)

Applicant's Study #:	RP-LID-PK001
Title	A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults under Fasted Conditions
Objectives	The primary objectives of this study were: • To assess the bioequivalence of a single 2100 mg dose (3 patches) of a test formulation of lidocaine 5% topical patch versus Lidoderm® after a 12-hour application in healthy adult male and female subjects under fasted conditions. • To assess the apparent dose delivered following application of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus Lidoderm® after a 12-hour application in healthy adult male and female subjects under fasted conditions. • To assess patch adhesive performance of a test formulation of lidocaine 5% topical patch versus Lidoderm® after a 12-hour application in healthy adult male and female subjects. The secondary objective of this study was: • To assess the safety and tolerability of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus Lidoderm® after a 12-hour application in healthy adult male and female subjects under fasted conditions.

Reviewer's comments:
Only the adhesion data were evaluated in this clinical review. Per DBII, the pharmacokinetic study is acceptable.

2.4.2.2.1 Protocol Review

Protocol Version	Protocol Date	IRB Approval Date
1	08/08/2013	08/16/2013

Reviewer's comments:
The study began on 09/04/2013, after the approval of the protocol on 08/16/2013.

2.4.2.2.2 Study Design

Overall Study Design and Plan
This is a randomized, open-label, two-period, crossover, single-dose fasted bioequivalence study and patch adhesion study. The adhesive property of Rhodes Pharmaceuticals L.P.'s lidocaine topical patches (test product) was compared to Lidoderm® (reference). During each period, three topical patches of an assigned treatment were applied simultaneously (2100 mg) to the infrascapular area of the back on either side of the spine, without occlusion, with approximately

2.5 cm between each patch for a total of 12 hours. Following a washout period of 7 days, subjects crossed over to the alternate reference (R) or test (T) formulation and the same procedures were performed at the same time points as noted for Period 1.

Table 2.11: Overall Study Design

Study/Protocol Number	RP-LID-PK001		
Subject Population	healthy adult male and female subjects		
Blinding	open-label study		
Randomization	treatment sequence		
Treatment arms	**Test**		**Reference**
Reinforced	no		
Number of period/phase	**Period 1**	**Rest**	**Period 2**
Duration	12 hours	7 days	12 hours
Dose administered	3 x 700 mg topical test or reference products applied simultaneously (2100 mg)	none	3 x 700 mg topical test or reference products applied simultaneously (2100 mg)
Dosing regimen	12 hrs	n/a	12 hrs
Number of applications	1	n/a	1
Application site	the infrascapular area of the back on either side of the spine, without occlusion, with approximately 2.5 cm between each patch	n/a	the infrascapular area of the back on either side of the spine, without occlusion, with approximately 2.5 cm between each patch
Adhesion assessment times	6 hours (± 30 min) following patch application and prior to patch removal	n/a	6 hours (± 30 min) following patch application and prior to patch removal

Reviewer's comments:

- *The applicant's study design is consistent with the draft product specific guidance. The draft product specific guidance recommends that adhesion scoring is to be done at least daily.*
- *The FDA's primary endpoint is the mean of adhesion scores at 6 hours (± 30 min) following patch application and prior to patch removal.*
- *The treatment administrations are consistent with the draft product specific guidance. Per RLD label, up to maximum of 3 patches can be applied at once up to 12 hours within a 24 hour period.*

Treatment Arms
Details of each treatment are provided in the table below.

Table 2.12: Treatment Arms (Study # RP-LID-PK001)

Treatment arms	Test	Reference
Product Name	Lidocaine Topical Patch, 5%	Lidoderm® (lidocaine) Topical Patch, 5%
Strength	5%	
Patch size	Whole patch: Length: 14 cm, Width: 10 cm	Whole patch: Length: 14 cm, Width: 10 cm
Manufacturer	Altergon	(b) (4) for Endo Pharmaceuticals
Batch/Lot No.	L1304191	Y2282
Manufacture Date	04/2013	n/a
Expiration Date	n/a	10/2015
Dosage Form	topical patch	
Route of administration	topical	

Reviewer's comments:
- *Test product lot # L1304191 is also used in irritation/sensitization study RP-LID-SSI.*
- *The composition and size of test product lot # L1304191 is the same as the to-be-marketed product.*

Study Population Selection
Study RP-LID-PK001 enrolled healthy volunteers aged 18 to 45 years of age. See applicant's study report, Section 9.2 (pages 23-25 of 143) for the full list of the applicant's inclusion and exclusion criteria.

Reviewer's comments:
- *The draft product specific guidance does not specify inclusion/exclusion criteria for the adhesion study. The applicant's inclusion/exclusion criteria are acceptable.*

Restrictions during the study	Subjects were not to apply topical products to or wash the back, or engage in strenuous activity during the 12- hour patch application period. On the day of dosing, subjects were not to consume any water within 1 hour before and 1 hour after patch application and were to remain fasted for at least 4 hours following patch application. Water was offered *ad libitum* after the 1-hour post-dose blood sample was collected. Water, soft drinks (sodas) without caffeine or non-citrus fruit juices were offered with meals and *ad libitum* beginning 4 hours post-dose. Subjects were to refrain from ingesting alcohol or caffeine within 24 hours prior to each dose. Subjects were to refrain from ingesting grapefruit products and grapefruit-containing juices within 72 hours prior to each dose.

Treatment compliance	All patches were applied by clinic personnel. The date and time study drug was administered to each subject were documented.

Reviewer comments

- *The applicant's restrictions during the study and treatment compliance assurance are acceptable.*

Assessments

The following adhesion scale was used during the study RP-LID-PK001:

Table 2.13: Patch Adhesion Scoring System

0 = ≥ 90% adhered (essentially no lift off of the skin)
1 = ≥ 75% to < 90% adhered (some edges only lifting off of the skin)
2 = ≥ 50% to < 75% adhered (less than half of the system lifting off of the skin)
3 = < 50% adhered by not detached (more than half the system lifting off of the skin without falling off)
4 = patch detached (patch completely off the skin)

Reviewer's comments:

The applicant's adhesion scale is consistent with the draft product specific guidance.

Endpoints

Primary Endpoint	mean adhesion scores

***Reviewer's comments**:*

The FDA statistical analysis used adhesion scores at 6 hours (± 30 min) following patch application and prior to patch removal for assessment of the cumulative adhesion score during the 12 hour application period. This is acceptable as the draft product specific guidance recommends adhesion scoring to be performed at least daily and in this case, the applicant evaluated at 6 hours and just prior to removal at the end of a 12-hour application.

Statistical Analysis Plan

See applicant's protocol, Section 13.1 (page 36-37 of 45) and FDA Statistical Review, Section 3.3.6.2 (pages 88 - 89) for details of the statistical analysis plan for details of the statistical analysis plan.

***Reviewer's comments**:*

All 48 enrolled subjects completed the study and were included in the applicant and FDA adhesion analyses.

This clinical reviewer did not recommend any changes to the applicant's adhesion population for the FDA analysis.

2.4.2.2.3 Study Subjects

Subject Disposition
Forty-eight (48) subjects, aged 18-45 years, were enrolled in RP-LID-PK001. Forty-eight (48) subjects completed the study.

Subjects Analyzed
The adhesion analysis cohort is the 48 subjects enrolled.

Demographics
The demographics of the PK BE/adhesion study RP-LID-PK001 are as follows.

		All Enrolled (N=48)
Gender	Female	23 (47.92%)
	Male	25 (52.08%)
Race	Black	19 (39.58%)
	White	29 (60.42%)
Age Group in Years	18-40	35 (72.92%)
	41-64	13 (27.08%)
Age in Years	Mean, SD	31.96, 9.22
	Min, Max	18, 45
	Q1, Median, Q3	22, 31.5, 45

Source: FDA Statistical Report Table 63

Reviewer's comments:
The demographic distributions for gender, race, and age should have no impact on the adhesion of the test and reference products.

2.4.2.2.4 Results

Adhesion Results
The adhesion scores for each patch should be monotone over time. It is observed that out of a total of 288 patches in the PP population, 1 patch did not satisfy monotonicity of the adhesion scores. The FDA statistical reviewer performed the analyses by monotonizing the adhesion scores where at each time point the adhesion score of a patch is replaced by the highest adhesion score of the previous assessments if the current adhesion score is observed to be less than the adhesion score at any of the previous time points. This method is also known as the worst observation carried forward (WOCF).

Table 2.14: Primary Non-inferiority Analysis of Mean Adhesion Score (Monotonized) for Test vs. Reference Patches per FDA (RP-LID-PK001)

Variable	Hypotheses	LSmean Test (SE)	LSmean Reference (SE)	Estimate of $\mu_T - \mu_R$	One-Sided 95% Upper Confidence Bound
Mean Adhesion Score	H_0: $\mu_T - \mu_R > \delta$ H_1: $\mu_T - \mu_R \leq \delta$	0.5278 (0.1257)	1.1632 (0.1257)	-0.6354	-0.4075

Source: FDA Statistical Report Table 68

Table 2.15: Number and Percent of Test and Reference Patches with Each Monotonized Adhesion Score at Each Assessment (RP-LID-PK001)

Assessment Time	Treatment	Adhesion Score									
		0		1		2		3		4	
6 Hours	Test	109	(75.69%)	24	(16.67%)	9	(6.25%)	2	(1.39%)	0	(0.00%)
	Reference	79	(54.86%)	38	(26.39%)	9	(6.25%)	12	(8.33%)	6	(4.17%)
12 Hours	Test	86	(59.72%)	32	(22.22%)	11	(7.64%)	10	(6.94%)	5	(3.47%)
	Reference	44	(30.56%)	40	(27.78%)	22	(15.28%)	17	(11.81%)	21	(14.58%)

Source: FDA Statistical Report Table 66

Reviewer's comments:
According to the FDA statistical review, the adhesion study RP-LID-PK001 demonstrates non-inferior adhesion performance of the test product to the reference product.

2.4.3 Brief Statements of Skin Irritation, Sensitization and Adhesion Conclusions

2.4.3.1 Irritation Conclusion

The data submitted for study RP-LID-SSI demonstrate that the skin irritation potential of Rhodes Pharmaceuticals L.P.'s. Lidocaine Topical Patch, 5% is no worse than that of the RLD. Results from RP-LID-SSI are supported by other evidence from the application that supports the conclusion that the skin irritation potential of the Rhodes Lidocaine Topical Patch, 5% is no worse than that of the RLD; i.e., the difference in formulation (see Section 2.7 below) is not expected to be associated with a change in irritation or sensitization potential, and the observed safety profile has not raised unexpected concerns (see Section 2.5 below).

2.4.3.2 Sensitization Conclusion

No subject had potential sensitization reaction to either the test or the reference product in study RP-LID-SSI. Also refer to Section 2.4.3.1.

2.4.3.3 Adhesion Conclusion

The data demonstrate that the adhesive performance of Rhodes Pharmaceuticals L.P.'s. Lidocaine Topical Patch, 5% is at least as good as that of the RLD.

2.5 Comparative Review of Safety

2.5.1 Description of Adverse Events

2.5.1.1 Skin Irritation and Sensitization Study (RP-LID-SSI)

Of 248 subjects enrolled in the irritation and sensitization study RP-LID-SSI, 129 (52.0%) subjects reported at least one adverse event. Most adverse events were mild or moderate in intensity. Three subjects experienced serious adverse events unrelated to the study drug and discontinued the study. Three subjects reporting a serious adverse event (SAE) had asthmatic bronchitis and acute upper respiratory infectio (b) (6) myocardial infarctio (b) (6) and left side radiculopathy (b) (6) One subjec (b) (6) had a papular rash on the back an en prior to patch application for the challenge p . No death was reported. The most frequently occurring adverse events were application site pruritus (42.3%), headache (6.9%), application site pain (5.2%), and back pain (3.6%). Because the applicant collected application site reactions without specifying treatment arm, it was not possible to compare the incidence of application site adverse events between test and reference products.

Please see Table 2.16 below for the applicant's safety population incidence of adverse events.

Table 2.16: Incidence of Adverse Events – Applicant Safety Population

Body System / Adverse Event	Reported Incidence by Cohort and Overall Study No. RP-LID-SSI		
	Cohort 1 N= 123 n (%)	Cohort 2 N= 125 n (%)	Overall N= 248 n (%)
Cardiac disorders	0	1 (0.8)	1 (0.4)
Myocardial infarction	0	1 (0.8)	1 (0.4)
Gastrointestinal disorders	3 (2.4)	3 (2.4)	6 (2.4)
Abdominal pain	2 (1.6)	0	2 (0.8)
Constipation	1 (0.8)	0	1 (0.4)
Diarrhoea	1 (0.8)	0	1 (0.4)
Dry mouth	1 (0.8)	0	1 (0.4)
Flatulence	1 (0.8)	0	1 (0.4)
Toothache	1 (0.8)	1 (0.8)	2 (0.8)
Vomiting	0	2 (1.6)	2 (0.8)
General disorders and administration site conditions	45 (36.6)	64 (51.2)	109 (44.0)
Application site pain	7 (5.7)	6 (4.8)	13 (5.2)
Application site pruritus	43 (35.0)	62 (49.6)	105 (42.3)
Fatigue	0	3 (2.4)	3 (1.2)
Immune system disorders	1 (0.8)	0	1 (0.4)
Hypersensitivity	1 (0.8)	0	1 (0.4)
Infections and infestations	1 (0.8)	8 (6.4)	9 (3.6)
Bronchitis	1 (0.8)	0	1 (0.4)
Upper respiratory tract infection	0	1 (0.8)	1 (0.4)
Viral infection	0	7 (5.6)	7 (2.8)
Musculoskeletal and connective tissue disorders	5 (4.1)	10 (8.0)	15 (6.0)
Arthralgia	0	1 (0.8)	1 (0.4)
Back pain	3 (2.4)	6 (4.8)	9 (3.6)
Muscle spasms	1 (0.8)	0	1 (0.4)
Musculoskeletal discomfort	1 (0.8)	0	1 (0.4)
Neck pain	0	1 (0.8)	1 (0.4)
Pain in extremity	0	3 (2.4)	3 (1.2)
Nervous system disorders	9 (7.3)	10 (8.0)	19 (7.7)
Dizziness	2 (1.6)	1 (0.8)	3 (1.2)
Headache	8 (6.5)	9 (7.2)	17 (6.9)
Radiculopathy	0	1 (0.8)	1 (0.4)

Psychiatric disorders	3 (2.4)	0	3 (1.2)
Dysphoria	1 (0.8)	0	1 (0.4)
Euphoric mood	1 (0.8)	0	1 (0.4)
Insomnia	1 (0.8)	0	1 (0.4)
Mood swings	1 (0.8)	0	1 (0.4)
Renal and urinary disorders	0	1 (0.8)	1 (0.4)
Nephrolithiasis	0	1 (0.8)	1 (0.4)
Reproductive system and breast disorders	1 (0.8)	1 (0.8)	2 (0.8)
Dysmenorrhoea	1 (0.8)	1 (0.8)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	2 (1.6)	3 (2.4)	5 (2.0)
Asthma	1 (0.8)	0	1 (0.4)
Oropharyngeal pain	1 (0.8)	3 (2.4)	4 (1.6)
Skin and subcutaneous tissue disorders	2 (1.6)	2 (1.6)	4 (1.6)
Pruritus	1 (0.8)	1 (0.8)	2 (0.8)
Pruritus generalised	0	1 (0.8)	1 (0.4)
Rash papular	1 (0.8)	0	1 (0.4)
Vascular disorders	1 (0.8)	0	1 (0.4)
Hot flush	1 (0.8)	0	1 (0.4)
Total	**53 (43.1)**	**76 (60.8)**	**129 (52.0)**

Source: Applicant Study Report Table 13

Reviewer's comments:
Application site related events occurred in 44% of enrolled subjects. Forty two percent of enrolled subjects had application site pruritus, which is expected from this type of study design. Because the applicant did not collect treatment arm information related to application site adverse events, this reviewer could not compare between products. Other systemic adverse events reported in this study have been reported similar to those in the RLD labeling.

SAEs, Including Death
No subjects died during this study. SAEs are listed below.

Table 2.17: Subjects Reporting an SAE

Subject	Cohort	Phase	SAE Reported	SAE Onset	SAE Resolution
(b) (6)	1	Induction	Asthmatic bronchitis and acute upper respiratory infection	(b) (6)	(b) (6)
	2	Challenge	Myocardial infarction		
	2	Induction	Left side radiculopathy		Not yet recovered[1]

Note: Cohort 1 was initiated in August and completed in September.
Cohort 2 was initiated in November and completed in December.
[1]Clinic attempted to follow up after discharge from the hospital for 30 days with no success.

Source: Applicant Study Report Table 14

Reviewer's comments:

- *Due to SAEs, three subjects were discontinued from the study. This reviewer agrees with the investigator's assessment that those 3 SAE are not related to the study drug.*

Pregnancy
No subject became pregnant during this study.

2.5.1.2 Pharmacokinetic/Skin Adhesion Study (RP-LID-PK001)

Of 48 subjects enrolled in pharmacokinetic adhesion study, two (4.2%) subjects reported at least one TEAE following administration of test product and no subject reported any TEAE following administration of the reference product.

Subjec (b) (6) reported dizziness and subjec (b) (6) reported headache, nausea and vomiting. These AEs were considered mild in intensity, possibly related to study drug, and were resolved without residual effects or any action taken.

There were no application site related AEs reported in this study.

Significant Adverse Events, Including Death
none

TEAEs that led to study drug discontinuation
none

Pregnancy
There were no pregnancies reported for Study RP-LID-PK001.

Table 2.18: Incidence of Adverse Events – Applicant's Safety Population

Body System / Adverse Event	Reported Incidence by Treatment Group Fasted Bioequivalence Study No. RP-LID-PK001	
	Test N=48 n (%)	Reference N=48 n (%)
Gastrointestinal disorders	**2 (4.2)**	**0**
Nausea	1 (2.1)	0
Vomiting	1 (2.1)	0
Nervous system disorders	**2 (4.2)**	**0**
Dizziness	1 (2.1)	0
Headache	1 (2.1)	0
Total	**2 (4.2)**	**0**

Source: Applicant Study Report Table 12-1

Reviewer's comment: *The incidence of adverse events reported in the test group is low and consistent with the RLD labeling. No application site related adverse events were observed from a single application 3 patches for 12 hours in both test and reference groups.*

2.5.2 Brief Statement of Safety Conclusions

The systemic AE profile for the test product is acceptable.

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Office of Study Integrity and Surveillance

A routine inspection was requested by OSIS on 04/20/2016 for irritation/sensitization study RP-LID-SSI. The OSIS inspection occurred from 10/17/2016 through 10/22/2016. Per OSIS memo dated 05/19/2016, OSIS declined to inspect the in vivo PK BE study with adhesion component based on acceptable inspection history. OSIS EIR dated 12/08/2016 observation #2 pertained to irritation and sensitization study RP-LID-SSI noted the following:

"An investigation was not conducted in accordance with the investigational plan. Specifically, in clinical study number RP-LID-SSI, 12 study subjects with patches that had completely fallen off (Class 4) were given Make-up Visits at the end of the study, when the study protocol only required study subjects that had greater that 50% of the patch fallen off, but not completely fallen off (Class 3), to have a make-up visit."

OSIS recommended that clinical study data be accepted for further Agency review, except for subjec(b) (6) OSIS recommended data from subject (b) (6) (b) (6) be excluded from per protocol analysis due to a protocol deviation. The inspection outcome was acceptable.

Due to applicant's protocol deviation related to "make-up" patches, FDA statistical reviewer performed subgroup analysis excluding all subjects who had the same issue as identified by the OSIS. Based on the FDA statistical result, the study outcome remained the same.

Reviewer's comments:
Although OSIS recommended accepting data for the review for study RP-LID-SSI, the FDA statistical reviewer identified numerous inconsistent irritation scores from the original dataset compared to subsequent datasets submitted in response to their ECD requests. Thus, DCR primary reviewer is concerned with data quality.

2.6.2 Office of Biostatistics

See FDA Statistical Review[5]

Reviewer's comments:

[5] http://panorama.fda.gov/task/view?ID=570ff5950007410d7a1b29ccd88d6ecc

The DCR primary reviewer agrees with the Office of Biostatistics conclusion.

2.7 Formulation

2.7.1 Product Design

	Generic Drug Product	RLD Product
Polymeric adhesive	Single polymer adhesive	Single polymer adhesive
Composition of Unit per area	Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains other inactive ingredients.	
Type	(b) (4)	(b) (4)
Size	10 cm x 14 cm	10 cm x 14 cm
Shape	rectangle	rectangle
Layers	3 layers	3 layers
Figure	No figure was found in the applicant's submission	No figure was found in the approved labeling of Lidoderm®
Dose delivered	700 mg of lidocaine	700 mg of lidocaine

2.7.2 Generic and RLD Components and Composition[6]

2.7.2.1 Test Formulation

Ingredient	Function	% Formula	Milligrams Per Patch
Lidocaine	Active ingredient	5.00	700
Purified Wate	(b) (4)		
Glycerin			
Sorbitol Solutio (b) (4)			
Polyacrylic Acid (b) (4)			
Sodium Polyacrylate			
Sodium Carboxymethylcellulose			
Propylene Glyco			
Urea			
Kaolin			
Tartaric Acid			
Gelatin			
Polyvinyl Alcohol (PVA)			

[6] OGD DBII review dated 05/11/2017 pages 35-37 of 43

	[redacted] (b) (4)		
Dihydroxyaluminium Aminoacetat			
Edetate Disodiu			
Methylparaben			
Propylparaben			
Total		**100.0**	

2.7.2.2 NDA 020612 Formulation

Ingredient	mg/g adhesive	mg/patch	[redacted] (b) (4)	Purpose
Lidocaine	50	700		active
[redacted] (b) (4)				[redacted] (b) (4)
Glycerin				
Sorbitol, 70%				
Polyacrylic acid 20% w/w				
Sodium polyacrylate				
Sodium carboxymethyl cellulose				
Propylene glycol				
Urea				
Kaolin				
Tartaric acid				
Gelatin				
Polyvinyl alcohol				
Dihydroxyaluminum aminoacetate				
Disodium edetate				
Methylparaben				
Propylparaben				
Total				

Reviewer's comments:
The test product and the RLD are qualitatively the same but quantitatively different. Except for sodium carboxymethyl cellulose and dihydroxyaluminum aminoacetate, all other inactive ingredients present in the test product were the same o [redacted] (b) (4) than those present in the RLD. According to DBII review dated 04/24/2017, a slight increase o [redacted] (b) (4) for sodium carboxymethyl cellulose in the test formulation compared to that in the RLD is not a safety concern and is acceptable based on the pharmacology/toxicology consult response. Sodium carboxymethylcellulose i [redacted] (b) (4) for example. In addition, for dihydroxy aluminum amino acetate, another ANDA 200675 (Lidocaine patch) approved on 08/23/2012 include [redacted] (b) (4) amount than the level proposed in the test formulation

[redacted]). *Thus, the DBII deems the test product acceptable. See DBII review for details.*

2.8 Relevant findings from Secondary and Tertiary Reviewers

Based on data discrepancies observed by the FDA primary statistical reviewer for irritation scores in study RP-LID-SSI, DCR primary reviewer concluded that no adequate conclusion can be made from this study. As a result, DCR secondary and tertiary reviewers considered all relevant findings and based on weight of evidence approach, supported by other information available within submission as follows, DCR recommends approval of this application:

1. The applicant's test product is only quantitatively different from the RLD. Except for two inactive ingredients, sodium carboxymethylcellulose and dihydroxyaluminum aminoacetate, all other inactive ingredients present in the test formulation are qualitatively the same and are at levels same or [redacted] those of the RLD. DBII determined that the amount of dihydroxyaluminum proposed in the test product is within the level of an approved Lidocaine patch for another generic applicant (ANDA 200675). Additionally, while dihydroxyaluminum aminoacetate is considered a potential skin irritant, the difference between the test and RLD patch amounts is small [redacted] and is not expected to be clinically significant. Regarding th [redacted] amount [redacted] of sodium carboxymethylcellulose present in the test product compared to the RLD, DCR determined that it is unlikely that thi [redacted] would affect the safety profile, as sodium carboxymethylcellulose is considered a non-irritating and non-sensitizing substance that is even used as a [redacted] Therefore, overall, DCR secondary and tertiary reviewers conclude that the minor differences in test formulation compared to the reference product do not pose any greater safety concern for irritation or sensitization potentials of the test product.
2. Per DBII, the test product is deemed to be bioequivalent to the RLD based on a pharmacokinetic study. In this same study, adhesion performance of the test product was shown to be acceptable.
3. Per FDA statistical reviewers, the applicant's datasets had inconsistent irritation scores that raised concerns regarding data integrity. Per OSIS, there were no significant findings observed for the irritation/sensitization study and data were considered acceptable for FDA review. Therefore, while DCR acknowledges the statistical review team's concerns with the data from study RP-LID-SSI, the lack of corroborating concerns from OSIS inspection makes it more difficult to justify completely disregarding study results.
4. Because the applicant's study design is significantly different from the recommendation provided in the drug specific guidance for this product due to inconsistent make-up patch use, FDA statistical reviewer performed 6 different study populations post-hoc to evaluate whether those protocol violations identified by the FDA statistical reviewer could change the study outcome. Based on FDA statistical reviewer's 6 different study populations analyzed, the study outcome remained the same, meeting non-inferiority criteria. Although the datasets may appear to be unreliable in some cases, overall assessment of datasets didn't present any bias or better irritation response toward the test product compared to the reference product.

The data discrepancies were mainly due to poor quality control. Taking into consideration that there is a low pre-test concern for irritation/sensitization, and no serious irritation/sensitization events in the development program, DCR secondary and tertiary reviewers conclude that this is adequate to support approval.

2.9 Conclusion and Recommendation

2.9.1 Conclusion

There is adequate information in ANDA 209190 to conclude that the minor differences in test formulation of Rhodes Pharmaceuticals L.P.'s Lidocaine Topical Patch 5% compared to the reference product, Lidoderm Topical Patch, 5%, does not pose any greater safety concern for irritation or sensitization potentials of the test product. The clinical data from Study RP-LID-PK001 demonstrate that the adhesive performance of Rhodes Pharmaceuticals L.P.'s Lidocaine Topical Patch, 5% is at least as good as that of the RLD, Lidoderm® (lidocaine) Topical Patch, 5%.

2.9.2 Recommendations

DCR recommends approval of this application, contingent on approval recommendations from the other disciplines on the review team.

3 CLINICAL COMMENTS TO BE PROVIDED TO THE APPLICANT

The Clinical Discipline has completed its review of ANDA 209190 and has no comments at this time.

Sunny Tse

Digitally signed by Sunny Tse
Date: 6/19/2017 01:32:55PM
GUID: 508da6ff0002855c7da84880bd716ed2

Carol Kim

Digitally signed by Carol Kim
Date: 6/19/2017 02:11:16PM
GUID: 508da70a00028df5288765ab0807f9a5

Sarah Yim

Digitally signed by Sarah Yim
Date: 6/19/2017 02:39:19PM
GUID: 50841a8900009e1fe2b0e31699e4e531

Division of Clinical Review Consultation

Lidocaine Topical Patch, 5%

Drug Product:	Lidocaine Topical Patch, 5 %
ANDA:	209190
ANDA Applicant:	Rhodes Pharmaceuticals, L.P.
Reference Listed Drug (RLD) **NDA, Approval Date** **RLD Sponsor:**	Lidoderm® (lidocaine) patch 5% NDA 020612, Approved on 03/19/1999 Teikoku Pharma, USA Inc.
Pharmacology-Toxicology Primary Reviewer:	Mi Young Yang, PhD Pharmacologist, Division Of Clinical Review (DCR) Office of Bioequivalence (OB) Office of Generic Drugs (OGD)
Medical Officer Primary Reviewer:	Mónica L. Fiszman, MD, PhD Clinical Reviewer DCR,OB,OGD
Medical Officer Secondary Reviewer:	Lolita Lopez, MD Clinical Team Leader DCR,OB,OGD
Tertiary Reviewer	Daiva Shetty, MD Deputy Director DCR,OB,OGD
To:	Beena Mathew, Pharm.D. Division of Filing Review (DFR) Office of Regulatory Operations (ORO)
Reason for Consult:	Assess the safety of the excipient carboxymethylcellulose (CMC) sodium in the drug product at the levels proposed.
Date of Submission:	04/13/2016
Date of Consult:	04/28/2016
Date Assigned:	06/07/2016
Date of Completion:	05/10/2017
Conclusion:	DCR concludes that th (b) (4) CMC sodium (b) (4) in the proposed lidocain d to the RLD d additional safety concerns, and is acceptable from Clinical and Pharm/Tox perspectives.

1 Executive Summary:

This review addresses a consult from the Division of Filing Review (DFR) to evaluate the applicant's justification regarding the safety of the higher level of carboxymethylcellulose (CMC) sodium in the proposed generic lidocaine 5% patch compared to the RLD, submitted under ANDA 209190 by Rhodes Pharmaceuticals L.P. The RLD, Lidoderm® Topical Patch 5% was approved for the relief of pain associated with post-herpetic neuralgia on 03/19/1999 (NDA 020612, sponsor: Teikoku Pharma USA Inc.) Each patch contains 700 mg of lidocaine.

According to the RLD's label, patients may apply up to three patches in a 24-hour period. The proposed patch contains CMC sodium [redacted] (b) (4) . The RLD contains [redacted] (b) (4) . Therefore, amount of CMC sodium in the proposed formulation i [redacted] (b) (4) compared to the RLD. The MDE for the proposed product is also [redacted] (b) (4) than any product listed in the FDA IID Database with similar conditions of use.

DCR evaluated CMC sodium in the proposed lidocaine topical patch from clinical safety and pharm/toxicology perspectives. The applicant's justification, FDA databases and other sources were reviewed for information relevant to this consult.

CMC sodium is the sodium salt of a polycarboxymethyl ether of cellulose. It is generally recognized as safe (GRAS) as a miscellaneous and general purpose food additive without limitations when used in accordance with good manufacturing practice (21CFR 182.1745). Applied locally, CMC sodium is considered as a non-irritating and no sensitizing substance. There are no published clinical studies reporting adverse events with CMC sodium applied topically to the skin. The World Health Organization (WHO) determined as "not specified" the Acceptable Daily Intake (ADI) for total cellulose derivatives because WHO considered that no toxic effects maybe expected even after high intakes.

The Applicant submitted two clinical studies to support approval of the ANDA; a skin irritation/sensitization study (Study RP-LID-SSI) which is under review by the ANDA review team in DCR, and a bioequivalence study (Study RP-LID-PK001) is under review by the Division of Bioequivalence. The adequacy and acceptability of the study conduct and results are pending review.

From a pharm/tox perspective, the non-clinical data indicates that the proposed level of sodium CMC in the generic version of lidocaine patch is within safe range compared to the RLD.

Based on available information, it is unlikely that a [redacted] (b) (4)) in the amount of CMC sodium in the proposed formulation compared to the RLD would affect the safety profile of the proposed formulation.

2 Recommendation:

From a clinical safety and Pharm/Tox perspectives, DCR concludes that the amount of carboxymethylcellulose (CMC) sodium in the proposed generic lidocaine patch 5% is acceptable. The amount of CMC sodium [redacted] (b) (4) in the proposed patch is unlikely to pose an increased safety risk to the patient if the generic drug product is used as a therapeutic equivalent of the RLD.

DCR has no recommendations to be conveyed to the applicant from a clinical safety and Pharm/Tox perspectives.

3 Regulatory Background:

The RLD, Lidoderm® (lidocaine patch 5%) was given orphan drug designation on 10/24/1995 for the indication of the relief of allodynia (painful hypersensitivity) and chronic pain associated with post-herpetic neuralgia[1]. It was subsequently approved by FDA for marketing for the relief of pain associated with post-herpetic neuralgia on 03/19/1999 (per Orange Book and DARRTS) under NDA 020612 (sponsor: Teikoku Pharma USA).

On 04/14/2016, Rhodes Pharmaceuticals L.P. (Rhodes), the applicant, submitted ANDA 209190 for a generic lidocaine patch 5%, the RLD is Lidoderm®. The applicantion included two studies to support approval of the ANDA: a skin irritation/sensitization study (Study RP-LID-SSI) which is reviewed by the ANDA review team in DCR, and a pharmacokinetic (PK) bioequivalence (BE) study (Study RP-LID-PK001) is reviewed by the Division of Bioequivalence II (DB II). Both studies are currently under review.

The proposed patch contains the excipient carboxymethylcellulose (CMC) sodium that i (b) (4) than the amount present in the RLD. DFR sent a consult to DCR stating the amount of excipient in the proposed product could not be justified by the IIG database, MDD, or RLD formulation, and requested evaluation of the Pharm/Tox data submitted by the applicant.

3.1 Current or Draft Guidance

There is product specific bioequivalence guidance for lidocaine topical patch, 5% at the "Bioequivalence Recommendations for Specific Products" website:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf (last revision, January 2016)

Active Ingredient: Lidocaine
Dosage Form: Route: Patch; topical
Recommended Studies: ***Three*** studies

1. Type of study: Fasting
   Design: Single-dose, in vivo, using three topical patches
   Strength: 5%
   Subjects: Normal healthy males and females, general population.
   Additional Comments:
   - Apply three topical patches simultaneously over a 12-hour period.
   - You may use fewer patches, provided the plasma concentrations of lidocaine are measurable to adequately characterize the pharmacokinetic profile of lidocaine for bioequivalence (BE) assessment based on the 90% confidence interval criteria.
   - Please include a 24-hour post-dose sampling time in the BE study.
   - In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. Analyze and include in the calculation the amount of adhesive residue from each patch left on the skin.

[1] FDA Intranet-Search Orphan Drug Designations and Approvals- Accessed on 08/ 08/2016
http://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=92395

2. Type of study: Adhesion study
   Design: Randomized, single-dose, two-treatment in vivo
   Strength: 5%
   Subjects: Healthy males and females, general population.
   Additional comments: Specific recommendations are provided below.

3. Type of study: Skin irritation and sensitization study
   Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 5% (administered as one-fourth of the test and one-fourth of the reference)
   Subjects: Healthy males and females, general population.

***Reviewer's comments**: The product specific guidance for lidocaine 5% patch recommends three studies as listed above. As mentioned earlier, the firm conducted two (instead of three) studies as recommended by the guidance, a PK/BE study and an irritation and sensitization study. Instead of conducting a separate adhesion study (see item 2 above), the applicant included an adhesion assessment in their BE study RP-LIDPK001 study.*

3.2 Orange Book Information

There are three marketed prescription entries in the Orange Book for Lidocaine, Topical Patch 5% (see Table 1 below). Lidoderm Patch 5%, NDA 020612 has RLD designation.

Table 1: Orange Book Currently Approved Applications for Lidocaine, Topical Patch 5% (n= 3)

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020612	AB	Yes	Lidocaine	Patch; Topical	5%	Lidoderm	TEIKOKU PHARMA USA
A202346	AB	No	Lidocaine	Patch; Topical	5%	Lidocaine	MYLAN TECHNOLOGIES
A200675	AB	No	Lidocaine	Patch; Topical	5%	Lidocaine	ACTAVIS LABS UT INC

Source: Search on 08/02/16 by this reviewer of the on-line Orange Book
TE=Therapeutic Equivalence
RLD=Reference Listed Drug

3.3 RLD Formulation

The RLD, Lidoderm® patch (NDA 020612), formulation is presented in Table 2.

Table 2: Formulation of Lidoderm Topical Patch 5%[2, 3]

Ingredients	Function	Potency (%)	Lidoderm® Weight (mg)/Patch
Lidocaine, USP	Active	5.00 %	700
Gelatin, NF	(b) (4)		
Edetate Disodium, USP			
Glycerin, NF			
D-Sorbitol, NF			
Kaolin, NF			
Sodium Polyacrylate			
Carboxymethylcellulose Sodium, NF			
Polyacrylic Acid			
Dihydroxyaluminum Aminoacetate, USP			
Propylene Glycol, NF			
Polyvinyl Alcohol, NF			
Tartaric Acid, NF			
Methylparaben, NF			
Propylparaben, NF			
Urea			
(b) (4)			

3.4 Proposed Generic Formulation

The proposed generic formulation was obtained from Section 3.2.P.1 in the application submission dated 04/13/2016[4].

Table 3: Composition of Lidocaine drug Product (ANDA 209190)

Ingredients	Function	Potency (%)	LIDODERM® Weight(mg)/Patch
Lidocaine, USP	Active	5.00 %	700
Glycerin, NF	(b) (4)		
D-Sorbitol, NF			

[2] NDA 020612/ S10-DARRTS, 12/28/2006, CMC Review (Table 1)
[3] ANDA 203265, DARRTS, 8/8/2012, CONSULT REV-NONCLINICAL-01- Emami, Armaghan
[4]ANDA 209190 \\cdsesub1\evsprod\anda209190\0000\m3\32-body-data\32p-drug-prod\lidocaine\32p1-desc-comp\description-and-composition.pdf

Polyacrylic Acid	(b) (4)
Carboxymethylcellulose Sodium, NF	
Sodium Polyacrylate Starch	
Propylene Glycol, NF	
Urea, USP	
Kaolin, NF	
Tartaric Acid, NF	
Gelatin, NF	
Polyvinyl Alcohol, NF	
Dihydroxyaluminum Aminoacetate, USP	
Edetate Disodium, USP	
Methylparaben, NF	
Propylparaben, NF	

Reviewer's comments: *The proposed formulation is qualitatively the same, only the amounts for few ingredients differ in minor percentages; polyvinyl alcohol amount is slightl* (b) (4) *in the RLD* (b) (4) *) compared t* (b) (4) *(proposed); dihydroxyaluminum aminoacetate is slightl* (b) (4) *in the propose* (b) (4) *versu* (b) (4) *in the RLD. DCR is consulted for CMC sodium in the proposed formulatio* (b) (4) *the amount i* (b) (4) (b) (4) *than in the RLD Lidoderm 5% (700 mg patch).*

4 Labeling:

The current product label for Lidoderm® (lidocaine) patch 5% was approved on 01/07/2015. See the full label for additional details[5]. There is no black box warning.

4.1 Indications

Relief of pain associated with post-herpetic neuralgia.

4.2 Off-Label Uses

A search of the NIH Clinical Trial Website[6] retrieved the following off-label uses for lidocaine topical patch 5%: Neuropathic pain, low back pain, myofascial pain, osteoarthritis [OA], diabetic neuropathy, fractures, and carpal tunnel syndrome.

[5] Lidoderm Patch , Label – S012, 01/07/2015
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020612s012lbl.pdf
[6] https://clinicaltrials.gov/ct2/results?term=lidocaine+patch&Search=Search

Reviewer's comments: *In the majority of clinical trials the dose of lidocaine topical patch 5% was up to 4 patches applied topically once daily although the Lidoderm label recommends only up to 3 patches within 24 hours.*

4.3 Dosage and Administration

Apply Lidoderm to intact skin to cover the most painful area. **Apply the prescribed number of patches (maximum of 3)**, only once for up to 12 hours within a 24 hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch (es) and do not reapply until the irritation subsides.

When Lidoderm is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.
Lidoderm may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

(b) (4)

4.4 Contraindications

Lidoderm is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

4.5 Adverse Reactions

Application Site Reactions
During or immediately after treatment with Lidoderm (lidocaine patch 5%), the skin at the Site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Reviewer's comments*: Per label, application site reactions are generally mild to moderate and resolve spontaneously.*

Allergic Reactions
Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Other Adverse Events
Due to the nature and limitation of spontaneous reports in postmarketing surveillance, causality has not been established for additional reported adverse events including:
Asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia,

lightheadedness, metallic taste, nausea, nervousness, pain exacerbated, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.

4.6 Use in Specific Populations

Pregnancy, Labor and Delivery: The label states that Lidoderm has not been studied in pregnancy, and it should be used during pregnancy only if clearly needed. Lidoderm ® has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should Lidoderm be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
Geriatric Use: The label makes no comment about geriatric use.

5 Discussion:

DCR was consulted by DFR regarding the level of the excipient carboxymethylcellulose (CMC) in the proposed generic lidocaine topical patch 5%. The proposed patch contains CMC sodium (b) (4) per patch while the RLD contain (b) (4) per patch, or an MDE Therefore, the amount of CMC sodium in the proposed formulation i (b) (4) than the amount present in the RLD.

DFR's consult request states *in-verbatim*:

> *"The above excipient(s) could not be justified by the IIG database, MDD, or RLD formulation.*
> *Please evaluate the Pharm/Tox data submitted in section 2.6.6: "Toxicology Written Summary" to determine if these inactive ingredient(s) are safe for use in this drug product at the levels proposed."*

5.1 Applicant's Justification

The Safety Assessment for CMC sodium submitted by Rhodes included preclinical data from the published literature on PK and toxicity after local administration and systemic exposure. The animal data are reviewed in Section 5.6 of this review.

For the clinical safety assessment, Rhodes referred to results of the two clinical studies submitted under ANDA 209190[7].

5.2 Brief Description of Excipient

Carboxymethylcellulose (CMC) sodium is the sodium salt of a polycarboxymethyl ether of cellulose. It contains NLT 6.5% and NMT 9.5% of sodium (Na), calculated on the dried basis. CMC sodium is also known as cellulose gum (CG).

[7] ANDA 209190-Section 2.6.6. CMC Safety Review-Page 10-11. \\cdsesub1\evsprod\anda209190\0000\m2\26-nonclin-sum\sod-cmc-saf-rev.pdf

Cosmetic Use[8]: The cellulose derivatives are used in a wide variety of cosmetics and toiletries as thickeners, suspending agents, film formers, stabilizers, emulsifiers, emollients, binders, or water-retention agents. Generally, the majority of uses are in hair products, eye and facial makeups, and skin care preparations. The concentration of use can range up to 10%. However, the celluloses are most frequently used in concentrations of >0.1-1 %. In 1981, CG was used in a total of 812 formulations, most of which were eye and skin makeup and skin care preparations. Of these 812, 11 % incorporated CG at unreported concentrations; 73% at concentrations of >0.1-1 %; 13% at concentrations <0.1 %; and 3% at concentrations of > 1-5%.
Non-cosmetic Use: CG is used in the pharmaceutical industry as a tablet excipient, suspending and viscosity increasing agent, bulk laxative, demulcent, dental adhesive, and as an absorption medium.

Synonyms[9]: Akucell; Aqualon CMC; Blanose; Carbose D; carmellosum natricum; **cellulose gum**; **CMC sodium**; Dynacel; E466; Finnfix; KiccolateNymcel ZSB; SCMC; **sodium carboxymethylcellulose**; sodium cellulose glycolate; Sunrose; Tylose CB; Tylose MGA; Walocel C; Walocel CRT; Xylo-Mucine.

5.3 Maximal Daily Dose (MDD) and Maximal Daily Exposure (MDE) Calculations

MDD: According to the label, patients may apply up to **three patches** in a 24-hour period. The proposed patch contains 700 mg of lidocaine, which results in an MDD of 700 mg x 3 patches = 2100 mg.

(b) (4)

5.4 Excipient in FDA Approved Drug Products

Excipient CMC Sodium as Active Ingredient

CMC sodium is an active ingredient listed under 21 CFR 349.12 for as ophthalmic demulcent for over-the-counter (OTC) human use at concentrations between 0.2 to 2.5 % [10]. CMC sodium ophthalmic solution is indicated [11]*for the temporary relief of burning, irritation, and discomfort due to dryness of the eye or exposure to wind or sun. For use as a protectant against further irritation or to relieve dryness of the eye, for use as a lubricant to prevent further irritation or to*

[8] American College of Toxicology, Final Report on the Safety Assessment of Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum, *International Journal of Toxicology*, 5, 1-59 (1986)
[9] Carboxymethylcellulose Sodium: Handbook of Inactive Ingredients, accessed on 8/9/2016 https://www.medicinescomplete.com/mc/excipients/current/1001935347.htm?q=carbomellose&t=advanced&ss=mn&tot=23&p=3#_hit
[10] 21 CFR §349.12 (Ophthalmic demulcents) http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=3609b77b584ae7a912583b8759e0ca8c&h=L&mc=true&n=pt21.5.349&r=PART&ty=HTML#se21.5.349_112
[11] 21 CFR §349.60 Labeling of ophthalmic demulcent drug products http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=3609b77b584ae7a912583b8759e0ca8c&h=L&mc=true&n=pt21.5.349&r=PART&ty=HTML#se21.5.349_112

relieve dryness of the eye[12]. The dose and administration is to*: Instill 1 or 2 drops in the affected eye(s) as needed and discard container.* OTC labels do not list adverse events.

Reviewer's Comments: *Conditions of use of this product (ophthalmic drops) differs from the proposed product (topical). In addition, the concentration of CMC sodium in this produc* (b) (4) *i* (b) (4) *than the CMC sodium concentration in the proposed formulation* (b) (4)

Excipient CMC Sodium as Inactive Ingredient

CMC sodium is an inactive ingredient used in FDA approved prescription drug products; the MDE in the proposed formulation for CMC sodium i (b) (4) An inactive ingredient search for CMC sodium was performed using the Inactive Ing atabase (IID). There are three approved transdermal systems, including the RLD (Lidoderm®, NDA 20612), that contain CMC sodium. The MDE of CMC sodium in the proposed formulatio (b) (4) the MDE for CMC sodium in the RLD and in FDA approved drug products as shown in Table 4. The proposed formulation ha (b) (4) CMC sodium compared to the RLD, Lidoderm.

Table 4: Search Results from the FDA Internal IID for Carboxymethylcellulose Sodium

Product (Application No)	Maximum Daily Dose	Indication	CMC sodium in drug product	Maximum Daily Exposure (MDE)
Proposed Formulation (Lidocaine 5%; ANDA 209190)	3 patches	Pain in post-herpetic neuralgia	(b) (4)	
RLD Lidoderm® (Lidocaine 5%; NDA 20612) -	3 patches	Pain in post-herpetic neuralgia		
Lidocaine (Lidocaine 5%; ANDA 200675)	3 patches	Pain associated with post-herpetic neuralgia		
Flector® (Diclofenac epolamine; NDA 21234)	2 patches	(b) (4)		

5.5 Clinical Evaluation

DCR reviewed the applicant's submission, FDA's Inactive Ingredient Database (IIG), Handbook of Inactive Ingredients, MERCADO, Code of Federal regulation (21 CFR), DARRTS, the Orange Book, the medical literature (Pubmed), RLD label and other databases for information relevant to this consult.

[12] Sodium CMC search in Dailymed (accessed on 8/9/2016)
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b32ed9e8-d091-4f16-b416-5a62cdfee49a

The Applicant submitted two clinical studies to support approval of the ANDA: a skin irritation/sensitization study (Study RP-LID-SSI) currently under review by the ANDA review team in DCR, and a pharmacokinetic/bioequivalence study (Study RP-LID-PK001) currently under review by the Division of Bioequivalence II (DB II).

5.5.1 Clinical Evaluation of the Applicant's Justification

Rhodes clinical justification [13] was based on the use of CMC sodium as a Generally Recognized as Safe (GRAS) food additive, and cited FAO/WHO and EU safety information. Rhodes also refers to the safety results from the BE study and the irritation and sensitization studies they submitted under ANDA 209190.

Rhodes states that CMC is commonly used as a viscosity enhancer of the drug-matrix solution in topical (dermal) pharmaceutical formulations and is also listed as an inactive ingredient in Lidoderm® (Lidocaine Patch 5%). Sporadic cases of sensitization associated with exposure to sodium CMC products have been reported in the literature. Sodium CMC is also listed as GRAS (Generally Recognized as Safe) direct food additive (21 CFR 182.1745) without limitations other than good manufacturing processes. The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1990) and the EU Scientific Committee for Food (SCF, 1992) had established an acceptable daily intake (ADI) for total cellulose derivatives for human consumption as "not specified" CMC is present in each proposed patch a (b) (4) At the maximal recommended daily dose of 3 patches, patient exposure to CMC in the patch could approach (b) (4) day if all the CMC was released. For an average patient (body weight of 60 kg), total osure to CMC could approac (b) (4) day.

Reviewer's comments*: The applicant's justification based on WHO and GRAS information are reasonable.*

The applicant makes reference to their conclusion of the two clinical studies they completed and submitted to the ANDA:

Irritation and Sensitization Study (RP-LID-SSI). This is an evaluation of skin irritation and sensitization potential of the 5% Lidoderm patch formulation in a panel of human volunteers following 21 days of exposure compared to the proposed product a repeat-insult patch test study in 248 subjects, 227 (91.5%) completed the study as designed. All subjects received test and RLD product simultaneously, with application sites randomly assigned. All applications of test and RLD product consisted of one-fourth of the patch. Rhodes concluded "There was no difference in skin irritancy indices, and skin sensitization analysis between Lidocaine 5% topical patch (Rhodes) and Lidoderm topical patch (RLD). Indeed, an analysis of individual cumulative irritancy and individual cumulative dermal response indices yielded identical scores for Lidocaine 5% topical patch and the Lidoderm topical patch. No patch was removed for either unacceptable skin irritancy or strong skin sensitization. Three (1.2%) subjects reported one serious adverse event; in the opinion of the Principal Investigator, these SAEs were unrelated to

[13] ANDA 209191 \\cdsesub1\evsprod\anda209190\0000\m2\26-nonclin-sum\sod-cmc-saf-rev.pdf . p.4

study test material. The study concluded that, Lidocaine 5% topical patches were safe and generally well tolerated in this normal, healthy adult male and female population."

Bioequivalence Study Study RP-LID-PK001. The bioequivalence of a single 2,100 mg dose of the proposed product was compared to the RLD product after a 12-hour application in healthy adult male and female subjects under fasted conditions (n=48). A secondary objective of this study was to evaluate the safety and tolerability of the test formulation of lidocaine 5% topical patch versus the RLD. The safety and tolerability of the lidocaine 5% topical patch were evaluated by the incidence of treatment-emergent adverse events, study discontinuation information, clinical laboratory test results, vital signs, skin irritation assessments, and physical examination findings. There were no serious adverse events reported during the study and no test subject discontinued treatment due to an adverse event. "It was concluded that, the test patches were generally safe and well-tolerated in this test population".

Overall, Rhodes concluded "Clinical information on the topical use of sodium CMC as a component of formulations indicates that there is a little if any risk for irritation or sensitization. Sporadic cases of sensitization associated with exposure to sodium CMC products have been reported in the literature. Clinical information on the Rhodes lidocaine (5%) patch has determined the potential for adverse local (and systemic) effects is no different from the RLD suggesting that the inclusion of sodium CMC at the stated amounts do not present a clinical risk. (Rhodes, 2013; 2014)."

Reviewer's comments: *As mentioned earlier, these studies are presently under review by OGD. The adequacy and acceptability of the study conduct and results will be determined by the review divisions in OGD.*

5.5.2 Safety Information in Humans from Published Medical Literature

No safety information was retrieved from the published literature (PubMed) for cellulose gum or carboxymethylcellulose (CMC) sodium applied topically to the skin. Three articles were retrieved from Pubmed for CMC sodium used as eye-drops. Reports state that CMC sodium ophthalmic solution is very well tolerated and effective for dry eye and postsurgical eye care[14,15,16]. Concentrations of CMC sodium tested in two reports were 0.5 and 1%.

Reviewer's comments: *The use of CMC sodium as eye drops cannot be used to support the safety of CMC sodium when applied to the skin topically because conditions of use differ from the proposed drug product. In addition, the concentration of CMC sodium for ophthalmic use is lower than in the proposed drug product.*

5.5.3 Safety Information in Humans from Other Sources

WHO[17,18]

[14] http://www.ncbi.nlm.nih.gov/pubmed/27422973
[15] http://www.sciencedirect.com/science/article/pii/S0886335015008494
[16] http://www.ncbi.nlm.nih.gov/pubmed/25880685
[17]WHO- Sodium Carboxymthylcellulose- http://www.inchem.org/documents/jecfa/jecmono/v26je08.htm

Humans: A new substantial body of human data was available investigating the laxative effects of modified celluloses which occurs in some subjects at levels as low as 5 g/person/day. At higher doses diarrhea has been reported in some subjects, but in others constipation developed. Studies in humans did not exceed the addition of 30 g/person/day. An intake of 30 g/day has been recommended as the upper safe level of dietary fiber in general.
Acceptable Daily Intake (ADI): The WHO committee initially established a group ADI of 25 mg/kg b.w. Information on the chemical structure, absorption, tissue distribution, excretion, metabolism and human exposure together with appropriate clinical observations suggested, that no true toxic effects could be expected even after high intakes, and then a numerical limitation of the ADI becomes unnecessary. JECFA in 1990 therefore allocated CMC, on the basis of these arguments, a group ADI of "not specified"[19], as had been done with other bulking food additives, to the seven modified celluloses evaluated in its 35th session.
The committee made, a general comment on the need to consider the possible laxative effect of an excessive total dietary consumption of all bulking agents, particularly in view of the additivity of this effect. It therefore suggested that some controls to limit consumption should be introduced. **The ability to produce laxation should be taken into account when using these substances as food additives.**

Reviewer's comment: *The concern for possible laxative effect described with CMC sodium administered orally will not impact the safety of the proposed formulation intended for topical use.*

Cosmetic Ingredient Review
The Amended Safety Assessment of cellulose and related polymers as used in cosmetics (Cosmetic Ingredient Review [20] (CIR)) for CMC sodium (search term cellulose gum) states in table 7 and page 31 states that repeated insult patch tests (RIPTs), single insult patch tests (SIPTs), cumulative irritancy tests, and maximization test have been conducted in clinics using Cellulose Gum, overall, was non-irritating and no sensitizing. Four hundred subjects were tested and the concentration was 100%.
FDA
According to the Code of Federal Regulations (CFR), 21CFR 182.1745, CMC sodium is Generally Recognized as Safe (GRAS) when used in accordance with good manufacturing practice[21] as a miscellaneous and general purpose food additive. The select Committee on GRAS Substances (SCOGS) stated *there is no evidence in the available information on sodium carboxymethyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard*

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[18]Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives (1989) http://www.inchem.org/documents/jecfa/jeceval/jec_1662.htm
[19] Definition of "not specified" http://apps.who.int/iris/bitstream/10665/37651/1/WHO_TRS_789.pdf page 45
ADI **"not specified"** means that, on the basis of the available data (chemical, biochemical, toxicological, and other), the total daily intake of the substance, arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary.
[20] Cosmetic Ingredient Review (search term Cellulose Gum) http://www.cir-safety.org/ingredients
[21] CFR Title 21 - Chapter I -Subchapter B - Part 182 -Subpart B-§182.1745 http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=6c47aae6cfff9271719814b805891815&ty=HTML&h=L&mc=true&r=SECTION&n=se21.3.182_11745

to the public when it is used at levels that are now current or that might reasonably be expected in future[22].

5.5.4 Summary Comments and Clinical Evaluation

- The content of CMC sodium in the proposed formulatio (b) (4) than the amount in the RLD (b) (4) It is als (b) (4) than any product listed in the FDA IIG Database with similar conditions of use.
- CMC sodium is generally recognized as safe (GRAS) as a miscellaneous and general purpose food additive when used in accordance with good manufacturing practice (21CFR 182.1745). Applied locally, CMC sodium is considered as a non-irritating and no sensitizing substance. No publication from the literature reports safety issues for CMC sodium applied topically to the skin.
- The WHO determined as "not specified" the ADI for CMC sodium because no true toxic effects maybe are expected even after high intakes.
- The Applicant submitted two studies to support approval of the ANDA: a skin irritation/sensitization study (Study RP-LID-SSI) and a pharmacokinetic bioequivalence study (Study RP-LIDPK001). Both studies are currently under review.
- DCR considers that th (b) (4) difference in the amount of CMC sodium between the RLD and the proposed formulation is small. It is unlikely that a sligh (b) (4) in the amount of CMC sodium in the proposed formulation compared to the RLD may affect the safety profile of the proposed formulation.
- The irritation and sensitization study results submitted under ANDA 209190 is still under review in OGD and should be considered when making a final safety determination about the proposed lidocaine patch.

5.6 Toxicology

The available FDA guidance, published information, and two safety review and assessment of carboxymethylcelluose (CMC) sodium reports provided by the applicant were reviewed from a Pharm/Tox perspective to assess the safety o (b) (4) of CMC sodium in the proposed generic lidocaine patch 5% (10 x 14 cm). CMC sodium is also known as cellulose gum (CG). This review evaluated the safety of CMC sodium based on the route of exposure. The nonclinical repeated dose toxicity studies using the oral route as well as dermal route were reviewed for system toxicity in the current review.

5.6.1 *Acute Toxicology*

Several studies have been performed in rats, guinea pigs and rabbits to assess the acute toxicity of CMC sodium with dermal and oral exposures[23]. The acute LD_{50} of CMC sodium by dermal application in rabbits was > 2000 mg/kg body weight. The acute oral LD_{50} values of CMC

[22] FDA GRAS Substances Database (Carboxymethylcellulose) accessed 08/08/2016 http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm261244.htm
[23] TOXNET at http://chem.sis.nlm.nih.gov/chemidplus/rn/9004-32-4

sodium in mice, rats, guinea pigs and rabbits were > 27000 mg/kg, > 27000 mg/kg, 16000 mg/kg, and > 27000 mg/kg body weight, respectively.

5.6.2 *Skin Sensitization*

CMC sodium was not sensitizing in the guinea pig[24].

5.6.3 *Absorption, Distribution, Metabolism and Excretion*

Due to the lack of the dermal absorption studies of CMC sodium, the studies of orally administered CMC sodium and its derivatives were evaluated to address the absorption, distribution, metabolisms and excretion properties of CMC sodium. The published literature indicates that cellulose derivatives pass unchanged through the gastrointestinal tract following oral administration in rats, dogs, and man[8]. Approximately 90% of fed CMC sodium was recovered in the rat feces[25] . In another experiment, radio-labelled 14C-CMC sodium was administered by oral gavage in rats following 2 weeks of pretreatment with unlabelled CMC sodium (500 mg/kg/day) admixed in the diet. Approximately 97% of the radioactivity was excreted (> 94% into the feces, and <1.83% into the urine) and < 1% of the radioactivity was retained in the body of rats[26] . However, only 50% of CMC sodium was recovered in the rabbit feces when rabbits were fed on diets containing CMC sodium[25].

5.6.4 *Genetic Toxicology*

Several studies, including Ames and chromosome aberration tests, have been conducted to address the mutagenic potential of CMC sodium and all data indicate that CMC sodium is not mutagenic[25]. Specifically, an Ames test with CMC sodium upto 5000 µg/plate was negative in Salmonella typhimurium either in the presence or absence of a liver metabolic activation system. In the chromosome aberration assay with Chinese hamster fibroblasts, CMC sodium was not genotoxic.

No evidence of carcinogenicity was observed after oral CMC sodium exposure for 2 years in several studies in mice and rats. This is discussed in more detail in the following section.

5.6.5 *Dermal Irritation*

A primary skin irritation test and a cutaneous tolerance test of CG were conducted on male albino rabbits[8]. For a primary skin irritation test, 1, 2 and 10% aqueous solutions of CG were applied on the both flanks, intact and abraded skins, and the degrees of irritation were read after 23 hour occlusion. The primary irritation indices ranged from 0 (1% and 10% CG) to 0.08 (4% CG) (max = 8) were nonirritating. For a cutaneous tolerance test, 1, 2 and 10% aqueous solutions of CG were applied on the clipped right and left flanks. Each group had 3 rabbits.

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[24] Avicel® RC-501 (microcrystalline cellulose and sodium carboxymethylcellulose) Material Safety Data Sheet, 2010

[25] WHO Food Additives Series 26 at http://www.inchem.org/documents/jecfa/jecmono/v26je08.htm

[26] Bar et al., Metabolic disposition in rats of regular and enzymatically depolymerized sodium carboxymethylcellulose*, Fd Chem. Toxic*., **33**(11), 901-907 (1995)

Each sample was speard uniformly by hand and given a light 30 sec-massage. Applications were made five times per week for 6 weeks. Recovery was observed for 7 days after the last application. Two biopsies taken from each rabbit at 6 weeks were examined microscopically. The mean maximum cutaneous irritation indices were 1 (1% CG, slightly irritating and relatively well tolerated), 0.67 (4% CG, slightly irriating and relatively well tolerated) and 0.34 (10% CG, nonirritating and well tolerated) (max = 8), indicating these samples were well tolerated.

In a 4-week skin irritation study, application of CG (unknown concentration) on the shaved abdominal area of rabbits five times per week for 4 weeks did not produce skin irritation[8].

5.6.6 *Repeated Dose Toxicology*

Due to the lack of the repeated dermal toxicity study of CMC sodium, two 13-week repeated dermal toxicity studies of product formations containing CMC sodium and the repeated oral toxicity studies of CMC sodium were evaluated to address the systemic toxicity of CMC sodium.

In a 13-week repeated dermal toxicity study, 886 mg/kg of a wrinkle smoother product containing 3% CMC sodium was applied on an anterior dorsal shaved site of each rat 5 days per week for 13 weeks by rubbing. Two control groups, untreated and ethanol treated groups, were compared to the treated group. The product was wiped off 1 hour after application because the active agent, sodium silicate, was a known irritant. No significant adverse effects were noted based on mortality, body weights, organ weights, hematological analysis, and gross and microscopic examiniation[8].

In another 13-week repeated dermal toxicity study, 2900 mg/kg of a lotion containing 1.1% CMC sodium was applied on an anterior dorsal shaved site of each rat 5 days per week for 13 weeks by rubbing. Control rats were treated with distilled water. No significant adverse effects were observed based on mortality, bodyweights, hematological values, and gross and microscopic examiniation[8].

Several repeated oral toxicity studies with CMC sodium have been performed in rats, guinea pigs, rabbits and dogs with durations ranging from 21 days to 1 year[25]. For example, rats received a diet containing 5% CMC sodium for 8 months and no toxic effects were observed. Rabbits were fed with the diets containing 4.8% and 9% of CMC sodium for two periods of 15 days without any notable toxic effects.

In a repeated oral toxicity study, 500 mg/kg and 1000 mg/kg of CMC sodium were administered to both white rats and dogs for 6 months while the same amounts of CMC sodium were given to guinea pigs for 6 months and 1 year. There was no test substance-related adverse effects in rats and guinea pigs which were treated for 6 months based on body weights, hematological analysis, and gross and microscopic examination. No significant adverse effects were oberved in guinea pigs exposed for 1 year and dogs exposed for 6 months based on body weight changes, and gross and microscopic examination[27].

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[27] Shelanski and Clark, Physiological action of sodium carboxymethylcellulose on laboratory animals and humans. *Food Res*., **13**, 29-35 (1948).

In a 90-day repeated oral toxicity study, CMC sodium was given to Albino Wistar rats in the diet (0, 2.5, 5 and 10% by weight) for 90 days. There were statistically significant increases of plasma alkaline phosphatase and alanine aminotransferase levels in 10% dosing group animals without histopathological hepatic changes. Water intake and urine production increased with increasing doses of CMC sodium due to the sodium content of CMC sodium. Some urinary parameters were altered. For example, changes in unirary pH and 24 hour urinary excretion of sodium of 5% and 10% dosing group animals were statistically significant compared to control groups and these changes were dose-dependent. Statistically significant urinary citrate excretion was noted in 10% dosing group compared to control group. The increased occurrence of nephrocalcinosis and hyperplasia of the urothelial epithelium in some of the treated groups was observed although these increases were not dose-dependent nor observed in both sexes. It could be an indirect consequence of an increase in urine alkalinity coupled with an increased calcium excretion. However, hyperplasia of urinary bladder noted in 10% dosing group animals was test substance -attributed. Treatment-related effects of diarrhea and cecal enlargement in 5% and 10% dosing groups were also observed. These changes are generally associated with the ingestion of non- or low-digestable compounds[28]. Therefore, the No Observed Adverse Effect Level (NOAEL) for 90-day oral subchronic toxicity is 2.5% by weight of diet in rats.

In a 2-year repeated oral toxicity, CMC sodium was given to rats (100, 500 and 1000 mg/kg body weight/day) in the diet for 2 years[27]. The body weights and haematological parameters were monitored monthly and histopathological analysis were conducted at the end of treatment. Monthly weight records indicated normal weight curves. There were no differences in haematological and microscopic examinations between treated and control animals. No neoplasms were found in experimental animals. Therefore, the NOAEL for 2-year oral chronic toxicity is 1000 mg/kg body weight in rats.

In another 2-year repeated oral toxicity, F344 rats received 5 mg/kg body weight of CMC sodium by gavage five days per week for 2 years[25]. Controls were untreated. Experimental animals were examined weekly for clinical signs and the presence of palpable lesions. Mean body weights were also monitored. Gross and microscopic examinations were performed on major organs and all gross lesions. Survival rates of CMC sodium treated animals were similar to those of controls. CMC-treated animals had approximately the same or fewer neoplasms than control animals. Therefore, the NOAEL for 2-year oral chronic toxicity is 5 mg/kg body weight in F344 rats.

In a 2-year repeated oral toxicity, CMC sodium was given to mice in the diets containing 0, 0.1 and 1% of CMC sodium for 100 weeks. There was no ovbious difference in mortality and tumour incidence between treated and control groups[25]. Therefore, the NOAEL for 2-year oral chronic toxicity is 1% by weight of diet in mice.

In another 2-year repeated oral toxicity, B6C3F1 mice received 50 mg/kg body weight of CMC sodium by gavage five days per week for 103 weeks[25]. Untreated mice served as controls. Experimental animals were examined weekly for clinical signs and the presence of palpable lesions. Mean body weights were also monitored. Gross and microscopic examinations were

[28] Bar et al., Subchronic Oral Toxicity Study with Regular and Enzymatically Depolymerized Sodium Carboxymethylcellolose in Rats, *Fd. Chem. Toxic.,* **33**, 909 – 917 (1995).

performed on major organs and all gross lesions. Survival rates of CMC sodium treated animals were similar those of controls. CMC-treated animals had approximately the same or fewer neoplasms than control animals. Therefore, the NOAEL for 2-year oral chronic toxicity is 50 mg/kg body weight in B6C3F1 mice.

5.6.7 *Reproductive Toxicology*

There was no reproductive toxicology study of CMC sodium by dermal administration. Instead, several reproductive toxicology studies by oral route of administration were evaluated to address reproductive toxicity of CMC sodium.

In a reproductive study, 20 male Sprague-Dawley rats received 200 mg/kg of CMC sodium for at least 60 days and 40 female rats received 200 mg/kg of CMC sodium for at least 14 days before mating and during a 6- day mating period by gavage. One half of treated female animals was continuously administered with 200 mg/kg CMC sodium until sacrifice on day 14 of gestation (total of 34 day-treatment). The remaining half of the females was continuously treated until weaning of the progeny at day 28 after birth (total of 62 day-treatment)[29]. Average body weights of parents (F0) were comparable for both treated and control groups although the body weight gain of CMC sodium-treated males was generally lower than that of controls. The body weight gain of offsprings (F1) was comparable for both treated and control groups. No treatment-related effects were observed in F0 based on the pregnancy ratio, the mean numbers of corpora lutea and implantation sites and the ratios corpora lutea/implantation sites. The duration of pregnancy and parturition was normal in the CMC sodium-treated group. The rate of resorptions, litter size and sex ratio in F1 were not significantly changed in the CMC sodium-treated animals. Nesting behavior (nursing, suckling and creeping), eye opening and pinna detachment were normal in CMC sodium-treated F1 animals. Behavioral test results of F1, including negative geotaxis, photophobotaxis and exploratory locomotion pattern in a cylindrical cage, were comparable for both the CMC sodium-treated and control groups. Therefore, the NOAEL was 200 mg/kg for fertility, reproductive performance and fatal development in rats.

In a teratogenicity study, pregnant Albino CD-1 outbred mice from days 6-15 of gestation received CMC sodium (0, 16, 74, 345, 1600 mg/kg/day) as a corn oil solution by gavage[25]. A positive control group of 24 pregnant mice received 150 mg aspirin/kg body weight/day. All pregnant females survived and no effects were observed on nidation or on maternal or fetal survival in CMC sodium-treated groups. The number of abnormalities seen in either soft or skeletal tissues of CMC sodium-treated groups did not differ from the number occurring spontaneously in sham-treated controls.

In another teratogenicity study, CMC sodium (0, 16, 74, 345, 1600 mg/kg/day) was given to pregnant Wistar-derived rats from days 6-15 of gestation as a corn oil solution by gavage[25]. 250 mg aspirin/kg body weight/day was administered to pregnant rats as a positive control. All pregnant females survived until the end of the study. No effects were observed on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of

[29] Fritz and Becker, The suitability of carboxymethylcellulose as a vehicle in reproductive studies, *Arzneimitteln Forschung,* **31**, 813-815 (1981).

CMC sodium-treated groups did not differ from the number occurring spontaneously in sham-treated controls.

5.6.8 *Risk Assessment*

The proposed amount of CMC sodium in the generic lidocaine 5% patch is 754 mg in each patch (5.39%). Therefore, the applicant's proposed maxmum daily exposure (MDE) would result in exposure to 2262 mg/day of CMC sodium based on the MDD in the RLD label (up to 3 patches within a 24 hour period) if all were released.

CMC sodium is listed as GRAS (Generally Recognized as Safe) direct food additive (21CFR 182.1745) when used in accordance with good manufacturing practice. CMC sodium is also used in cosmetic formulations, most of which were eye and skin makeup and skin care preparations. CMC sodium is considered inert for topical formulations and is not considered a human irritant or sensitizer[8].

CMC sodium is an inactive ingredient used in FDA approved drug products. An inactive ingredient search for CMC sodium was performed using the Inactive Ingredient Database (IID) and the results are presented in Table 4 (Section 5.4). There are three approved drug products, which are transdermal systems including the RLD (Lidoderm®, NDA 20612). However, the levels of CMC sodium in the drug products are lower than the current proposed limit. The current proposed limit for sodium CMC (i.e. 754 mg/patch) is 7.7% higher than the amount in the RLD (i.e. 700 mg/patch).

For the safety evalution of CMC sodium in the proposed generic product, the nonclinical data from the published literature were reviewed. Due to a limited availability of dermal toxicity studies of CMC sodium, several oral chronic toxicity studies were evaluated to address the systemic toxicity concern of CMC sodium.

CMC sodium was not mutagenic based on Ames tests. The absorption of orally administered CMC sodium is very limited and the majority of orally administered is excreted into feces. Dermal exposure of CMC sodium is also not expected to be bioavailable because CMC sodium is a high molecular weight polymer, which cannot penetrate the skin even ifall CMC sodium is released from the patch.

For local toxicity, dermal toxicity studies in rabbits indicate that CMC sodium upto 10% was not irritating for 4 week-repeated exposure.

For systemic toxicity, 1000 mg/kg/day of CMC sodium was not associated with any overt toxicity based on body weight, clinical pathology and histopathology in a two-year oral chronic toxicity study. Therefore, the NOAEL of CMC sodium for 2 year repeated dose toxicity in rats is 1000 mg/kg/day (human equivalent dose of 6000 mg/m^2/day with a body surface area conversion factor 6 for rat) which is 4.3-fold higher than the proposed MDE of 2262 mg/day (equivalent to 1394.9 mg/m^2, assuming an average human weighing 60 kg and using a body surface area conversion factor 37 for humans).

In the repeated oral dose toxicity studies, 1000 mg/kg/day of CMC sodium treatment of guinea pigs for one year and dogs for six months did not induce any detectable toxicity based on body weight, and gross and microscopic examination. Therefore, the NOAEL of CMC sodium in guinea pigs and dogs is 1000 mg/kg/day (human equivalent dose of 8000 mg/m^2/day in guinea pigs and 20000 mg/m^2/day in dogs with a body surface area conversion factor 8 and 20, respectively). The safety margins between the human exposure and the non-clinical exposure based on the one-year chronic toxicity study in guinea pigs and six-month chronic toxicity study in dogs are 5.7 (8000/1394.9) and 14.3 (20000/1394.9) respectively.

The safety margins seem reasonable enough and the proposed limit of CMC sodium is onl (b) (4) (b) (4) than the amount in the RLD. Therefore, the proposed amount of CMC sodium at the MDD for the proposed generic formulation of lidocaine patch is within the safe range.

Table 5: Toxicology Data Summary Table for CMC Sodium

Contaminant Name	CMC Sodium		
Drug	Lidocaine		
Dosage Form	Patch		
Route	Transdermal		
Strengths Available	5%		
Maximum Daily Dose	3 patches		
Dosage Strength	Contaminant (mg) / Unit Dose	Dosage Units at MDD	Excipient (mg) at MDD
5%	(b) (4)		
Study (reference)	**Shelanski and Clark, *Food Res.*, 13, 29-35 (1948)**	Shelanski and Clark, *Food Res.*, **13**, 29-35 (1948)	Shelanski and Clark, *Food Res.*, **13**, 29-35 (1948)
Route of Admin	**oral (in the diet)**	oral (in the diet)	oral (in the diet)
Duration (days)	**2 years**	1 year	6 months
Species	**Rats**	Guinea pig	Dogs
Effect Level	**NOAEL = 1000 mg/kg/day**	NOALE = 1000 mg/kg/day	NOAEL = 1000 mg/kg/day
BSA Conv.	**6000 mg/m^2/day**	8000 mg/m^2/day	20000 mg/m^2/day
Safety Factor(s)	**4.3 fold**	5.7 fold	14.3 fold

6 Conclusion:

From both clinical and pharm/tox perspectives, DCR concludes th (b) (4) difference in the amount of CMC sodium in the proposed generic lidocaine topical patch 5% (b) (4) does not appear to pose any additional safety concerns when compared to the RLD, Lidoderm® (2100 mg/day).

7 References:

7.1 Clinical

See footnotes

7.2 Toxicology

See footnotes

Monica Fiszman

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Mi Young Yang

Digitally signed by Mi Young Yang
Date: 5/10/2017 04:29:04PM
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Lolita Lopez

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Daiva Shetty

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Date: 5/11/2017 05:45:37AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

CHEMISTRY REVIEW(s)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Complete Response-Minor
☐ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA 209190
Assessment #4

Drug Product Name	Lidocaine Patch 5%
Dosage Form	Patch
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Rhodes Pharmaceuticals L.P.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD 1 Original	04/14/2016	Drug Product, Facilities
SD 3 Quality/Response to Information Request	05/23/2016	Drug Product, Facilities
SD 4 Response to IR	08/05/16	Facilities
SD 5 Response to ECD Bioequivalence	08/15/16	Facilities
SD 6 Response to ECD Clinical Bioequivalence	09/06/16	Facilities
SD 7 Response to ECD/Quality	09/29/2016	Drug Product, Process, Facilities
SD 10 Response to ECD/Quality	01/23/2017	Drug Product, Facilities
SD 12 Response to CR	09/26/2017	Drug Product, Microbiology, Biopharmaceutics,
SD 13 Response to CR	09/12/2018	Drug Product
SD 14 Response to CR	07/30/2019	Drug Product
SD 15 Response to Labeling	09/04/2019	Drug Product
SD 16 Response to IR	02/04/2020	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	N/A	N/A
Drug Product	Adchara Pongpeerapat	Brock Roughton
Manufacturing	Cassandra Abellard	Derek Smith
Microbiology	Yuansha Chen	Neal Sweeney
Biopharmaceutics	Kelly Nolen	Tapash Ghosh
Regulatory Business Process Manager	Fred Echoles	
Application Technical Lead	Brock Roughton	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

FDA U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

MFs:

	Type		Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	July 5, 2018	Assessed by Xinghua Wu
	Type III		(b) (4)	N/A		
	Type II			N/A		
	Type II			N/A		
	Type IV			Adequate	December 11, 2017	Assessed by Adchara Pongpeerapat
	Type IV			Adequate	February 4, 2020	Assessed by Adchara Pongpeerapat

THER D S *proved ANDA*

Documen	Application Number	Description
RLD	NDA 20612	Lidoderm (Lidocaine Patch 5%)

2. CONSULTS

Discipline	Status		Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	(b) (4)	April 29, 2019	Narendranath Reddy Chintagari

Pharmacology/ Toxicology	Complete	_____ (b) (4) [redacted]	Nov. 7, 2019	Narendranath Reddy Chintagari
Pharmacology/ Toxicology	Complete	_____ (b) (4) [redacted]	Sept. 23, 2019	Wei Ding
CDRH-ODE	N/A			
CDRH-OC	Complete	**Adequate:** Applicant's response to a design controls deficiency submitted on December 19, 2017 is adequate	Nov 5, 2018	M. Isabel Tejero del Rio
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY (APPROVALS ONLY)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product:

- The applicant has provided acceptable raw material, in-process, and finished product controls
- The applicant has accepted the in vitro drug release acceptance criteria recommended by Biopharmaceutics
- The Office of Pharmaceutical Manufacturing Assessment overall recommendation on all the manufacturing facilities is "Approve"
- The proposed expiry date of 36 months is acceptable
- The labeling has adequate quality information

Therefore, from a quality perspective, ANDA 209190 is recommended for approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The basis for the applicant's ANDA is the approved reference listed drug (RLD), Lidoderm (NDA 20612), listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book). The drug product is topical patch available in 5% strength containing 700 mg of lidocaine per patch. The drug product is packaged in individual child-resistant pouches.

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

**Only the drug substance has a USP monograph.*

Proposed Indication(s) including Intended Patient Population	Relief of pain associated with post-herpetic neuralgia

Duration of Treatment	Up to 3 patches worn for maximum of 12 hours per 24 hours
Maximum Daily Dose	2100 mg (cumulative drug content of 3 systems)
Alternative Methods of Administration	Patches may be cut into smaller sizes with scissors prior to removal of the release liner.

B. Quality Assessment Overview (Please note: ATLs should check the most recent policy alert list)

Drug Substance

Lidocaine is official in USP and EP. The drug substance specification agrees with the USP monograph. The applicant references DMF (b) (4) held by (b) (4)

(b) (4)

The labeling contains acceptable quality information.

outcome of the inspection, the firm's acceptable compliance history, and (b) (4) experience with transdermal product manufacturing. In addition, use of (b) (4) for testing of the drug product is acceptable.

Per the CDRH consult review memo, the drug product manufacturing facility (Altergon) was found acceptable. In addition, CDRH determined that the applicant has provided acceptable documentation of the facility's quality management system and design controls.

Biopharmaceutics
The applicant developed and validated an adequate in vitro drug release method. In addition, the firm's proposed drug release acceptance criteria are adequate based on the submitted drug release data.

The following drug release method and acceptance criteria are recommended for the test product and have been accepted by the applicant:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32ºC	500	10 minutes: NMT (b) (4) 30 minutes: (b) (4) 180 minutes: NLT (b) (4)

Microbiology

The product is non-sterile. The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>. The applicant commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (36 months).

Shelf Life Considerations

The applicant has provided 36 months of long-term stability results for batch manufactured on the (b) (4) intended to be used for commercial production. (b) (4) (b) (4) The proposed expiry date of 36 months is acceptable.

Policy Alert

(b) (4)

C. Risk Assessment

Drug Product CQAs	Initial Risk Ranking		Updated Risk Ranking After Assessment Cycle #4	
Physical stability (polymorphism and recrystallization)	Medium	(b) (4)	Low	(b) (4)
Physical stability (cohesive)	High		Low	
Physical stability (adhesive)	High		Low	

Drug Product CQAs	Initial Risk Ranking		Updated Risk Ranking After Assessment Cycle #4	
		(b) (4)		(b) (4)
Chemical stability	High		Low	
Assay	Medium		Low	
Content uniformity	High		Low	

Drug Product CQAs	Initial Risk Ranking		Updated Risk Ranking After Assessment Cycle #4	
		(b) (4)		(b) (4)
Drug release	Medium		Low	
Microbial limits	Low		Low	

Application Technical Lead Name and Date: Brock Roughton; March 2, 2020

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

LABELING

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

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

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

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

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

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

If "No," explain.

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

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

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

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

ANDA Strength	Length (mm)	Imprint Code

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

None

List of Deficiencies:

N/A

Primary Drug Product Reviewer Name and Date: Adchara Pongpeerapat, PhD, 1/24/17; 6/1/17

Secondary Drug Product Reviewer Name and Date: I concur with the above assessment.

Brock Roughton, PhD, 2/22/2017, 01-JUNE-2017

Adchara Pongpeerapat

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Brock Roughton

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PROCESS

Product Background:

ANDA:	209190
RLD:	NDA 20612 (Lidoderm®)
Drug Product Name / Strength:	Lidocaine topical patch, 5%
Route of Administration:	Topical
Applicant Name:	Rhodes Pharmaceutical L.P.

Product characteristics:

(b) (4)

(b) (4)

P.3 Manufacture

Batch Formula

Batch formula from P.3.2

Table 1 Batch Formula of Lidocaine Patch 5%

Ingredient	Function	(b) (4)
Lidocaine, USP	Active	
Purified water, USP	(b) (4)	
Glycerin, USP		
Sorbitol, USP (b) (4)		
Polyacrylic acid[1] (b) (4)		
Carboxymethylcellulose Sodium, USP		
Sodium polyacrylate[1]		
Propylene glycol, USP		
Urea, USP		
Kaolin, USP		

Table 1 Batch Formula of Lidocaine Patch 5%

Ingredient	Function	(b) (4)
Tartaric acid, NF		
Gelatin, NF		
Polyvinyl alcohol, USP		
Dihydroxyaluminum aminoacetate, USP[2]		
Edetate disodium, USP		
Methylparaben, NF[3]		
Propylparaben, NF[4]		
Total Patch Weight		
Total Batch Size		

(b) (4)

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Review cycle #1: James J. Norman 02/06/2017; 03/05/2017; 05/15/2017
Review cycle #2: James J. Norman 10/24/2017
Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Review cycle #1: Yubing Tang 03/04/2017, 03/05/2017 and 06/06/2017
Review cycle #2: Yubing Tang, 10/24/2017, 11/ 08/ 2017

James Norman

Digitally signed by James Norman
Date: 11/13/2017 12:55:18PM
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Yubing Tang

Digitally signed by Yubing Tang
Date: 11/13/2017 09:56:57PM
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(b) (4)

perform testing as outlined in the application.

CDRH CONSULT OUTCOME:

Per the CDRH consult review memo, the only manufacturing facility (Altergon) requiring review was found acceptable based on the 2016 PAI discussed above. However, the application is deficient from a documentation perspective. The CDRH deficiencies will be communicated in the Complete Response letter. Please see consult memo uploaded with the Facility IQA Chapter for details.

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

QUALITY ASSESSMENT

List of Deficiencies:

CDRH deficiencies documented in IR#2 were not responded to by applicant in adequate time per RBPM. See CDRH consult.

Amend-12: All responses were acceptable with exception of a CDRH inadequate response on Design Review. As the application is being CR'd due to multiple disciplines, this one item will be included in the CR. Facilities remain acceptable from CDER; No changes made from original review.

Primary Facilities Reviewer Name and Date:

C. Abellard 06/12/2017 Consumer Safety Officer- OPF/ DIA-BII

Amend 12: C. Abellard 11/13/2017

Secondary Reviewer Name and Date:

D. Smith 06/26/2017

Cassandra Abellard

Digitally signed by Cassandra Abellard
Date: 11/29/2017 08:36:59AM
GUID: 564f42da0022c9f20052124ea8956e48

Derek Smith

Digitally signed by Derek Smith
Date: 11/29/2017 08:16:21AM
GUID: 508da7480002bfe5d5fe14a12da3599d

MICROBIOLOGY

Product Background:

ANDA: 209190

Drug Product Name / Strength:
Proprietary: N/A
Non-proprietary: Lidocaine Patch 5%

Route of Administration: Topical patch

Applicant:
Name: Rhodes Pharmaceuticals L.P.
Address: 498 Washington Street, Coventry, Rhode Island 02816, USA

US Agent:
(b) (4)

Manufacturing Site:
Zona Industriale A.S.L.
Morra De Sanctis
Avellino 83040, Italy

Method of Sterilization: N/A. Drug product is non-sterile.

Review Summary:
The submission is recommended for approval from the Product Quality Microbiology review perspective.

List Submissions being reviewed (table):

Submitted	Received	Date assigned to reviewer
9/26/2017	9/26/2017	10/10/2017

Submission History (for 2nd Reviews or higher) N/A

Submit	Received	Reviewed
4/14/2016	4/14/2016	2/22/2017

Highlight Key Outstanding Issues from Last Cycle: Commitment to perform preservative effectiveness test at the end of the shelf life was not stated.

Concise Description Outstanding Issues Remaining: N/A

Product Quality Microbiology Assessment

This amendment responded to The Agency's complete response letter dated 7/7/2017.

Microbiological deficiencies from the last review cycle were conveyed to the applicant via a complete response letter dated 7/7/2017. Applicant's response was received on 9/26/2017. The original comment (in italics) and the applicant's response are included below.

Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (reference: Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products - Questions and Answers).

Response: Rhodes commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (36 months).

The applicant also provided the 36-month data for AET testing of the registration batch, Lot L1304191.

Log reductions w

Microorganisms			
S. aureus	(b) (4)		
P. aeruginosa			
E. coli			
C. albicans			
A. brasiliensis			

(b) (4)

Reviewer's Assessment: Preservativ
topical products.

Adequate

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.

CDER/OPQ/OPF/DMA

10/26/2017

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

Neal J. Sweeney, Ph.D.

CDER/OPQ/OPF/DMA

11/4/2017

Yuansha Chen

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Date: 12/05/2017 08:08:29PM
GUID: 545289f5000727e1136ef94794e114b8

Neal Sweeney

Digitally signed by Neal Sweeney
Date: 12/03/2017 09:12:22PM
GUID: 508da70c00028f5119acd77351f33159

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☒ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA 209190
Assessment #3

Drug Product Name	Lidocaine Patch 5%
Dosage Form	Patch
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Rhodes Pharmaceuticals L.P.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
(1) Original	*04/14/2016*	*All*
(3) Quality/Response to IR	*05/23/2016*	*DP, Process, Facility*
(7) Response to ECD/Quality	*09/29/2016*	*DP*
(10) Response to ECD/Quality	*01/23/2017*	*DP, Process, Facility*
(12) Response to CR	*26-SEPT-2017*	*All*
(13) Response to CR	*12-SEPT-2018*	*All*

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance		
Drug Product	Adchara Pongpeerapat	Brock Roughton
Manufacturing	Cassandra Abellard	N/A
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Fred Echoles	
Application Technical Lead	Brock Roughton	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

FDA U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

MFs:

	Type		Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	July 5, 2018	Assessed by Xinghua Wu
	Type III		(b) (4)	N/A		
	Type III			N/A		
	Type III			N/A		
	Type IV			Adequate	Dec. 11, 2017	Assessed by Adchara Pongpeerapat
	Type IV			Inadequate	April 9, 2019	Assessed by Adchara Pongpeerapat

THER DO S ***proved ANDA***

Document	Application Number	Description
NDA	20612	RLD

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	**Inadequate-Maior** (link to consult response): the (b) (4) pose safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective.	April 29, 2019	Narendranath Reddy Chintagari
CDRH-ODE	N/A			
CDRH-OC	Complete	**Adequate:** applicant's response to a design controls deficiency submitted on December 19, 2017 is adequate	Nov 5, 2018	M. Isabel Tejero del Rio
Clinical	N/A			
Other	N/A			

U.S. FOOD & DRUG ADMINISTRATION

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Major

The application is not recommended for approval due to quality related deficiencies summarized in Section II.E. OPQ recommends issuing a Complete Response Letter – **Major.**

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Adequate

Lidocaine is official in USP and EP. The drug substance specification agrees with the USP monograph. The referenced (b) (4) held by (b) (4) (b) (4) is adequate. Lidocaine exhibits one polymorphic form. The analytical methods are acceptable.

Drug Product: Inadequate-Major

1. Primary Justification:

Theme 1: Product safety
Justification 1: The drug product deficiencies have been classified as MAJOR because there is need for safety assessment of extractables and leachables, inadequate assessment of extractables and leachables, or submission of that assessment in an unsolicited amendment as noted in Appendix A, Section A(2)(o) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required for establishing safety of the drug product. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources.

2. Secondary Justification:

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

Lidocaine patch 5% is non-compendial. The drug product is topical patch with a (b) (4) similar to the RLD formulation. The formulation uses (b) (4) (b) (4)

The applicant has adequately mitigated the high risks identified in the initial quality risk assessment: chemical stability, physical stability (cohesive and adhesive), content uniformity, and solubility. The applicant has tightened the level of (b) (4) to an acceptable level. The proposed controls for (b) (4) are acceptable. The 36-month stability results show the (b) (4) trending in (b) (4) reaching the specification limit. The applicant should clarify the proposed expiration dating period. The applicant should demonstrate compliance with ICH Q3D.

The applicant has proposed control of adhesive impurities in the adhesive raw material. In addition, the applicant has adequately performed leachable studies and detected three leachables at toxicologically-relevant levels. To evaluate the safety and acceptability of (b) (4) (b) (4) do not pose any safety concern and are acceptable. However, the (b) (4) (b) (4) pose safety concern and are unacceptable from a pharm/tox perspective. DCR requests major deficiency for safety assessment of these impurities in the CR letter, placed below under the Pharmacology/Toxicology Deficiencies.

Labeling: Adequate

The labeling has acceptable quality information.

B. Manufacturing: Adequate

The applicant uses a standard process for producing (b) (4) topical patches. The main process steps are (b) (4) (b) (4) (b) (4) (b) (4)

(b) (4) manufactures and tests the drug substance. The last inspection of the facility was July 2016 and was classified VAI. The facility is acceptable because of the manufacturing history of this marketed API (over 10 years), the acceptable review of the DMF, and acceptable inspectional history. In addition, use of (b) (4) for testing of the drug substance is acceptable.

Altergon Italia S.r.l. (FEI# 3007086839) manufactures the drug product. The last inspection of the facility was performed November 2015 and was classified NAI. This facility is acceptable to manufacture this product because of the outcome of the inspection, the firm's acceptable compliance history, and experience with transdermal product manufacturing. In addition, use of (b) (4) (b) (4) for testing of the drug product is acceptable.

Per the CDRH consult review memo, the only manufacturing facility (Altergon) requiring review was found acceptable. In addition, CDRH determined that the applicant has provided acceptable documentation of the facility's quality management system and design controls.

C. Biopharmaceutics: Adequate

The applicant developed and validated an adequate in vitro drug release method. In addition, the firm's proposed drug release acceptance criteria are adequate based on the submitted drug release data.

The following drug release method and acceptance criteria are recommended for the test product and have been accepted by the applicant:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10 minutes: (b) (4) 30 minutes: (b) (4) 180 minutes: (b) (4)

D. Microbiology: Adequate

The product is non-sterile. The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>. The applicant commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (36 months).

E. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies – N/A

2. Drug Substance Deficiencies – N/A

3. Drug Product Deficiencies

1. We note that you have included elemental impurities in drug product specification. Please submit risk assessment and control of elemental impurities to demonstrate compliance with ICH Q3D. The information should include potential sources from raw materials, manufacturing equipment, container closure, water, etc.; identification of potential elemental impurities, and evaluation of the presence of elemental impurities in the drug product. The analytical methods should be able to detect potential elemental impurities and suitable for their intended purposes.

2. The Drug Master File (DMF) [redacted] (b) (4) has been reviewed and found inadequate. The DMF holder, [redacted] (b) (4) was notified of the deficiencies on April 10, 2019. Please consult with your DMF holder, and provide the updated relevant P.4 sections. Do not respond to this ANDA CR letter until you have confirmed that the DMF holder has responded to the DMF deficiency letter cited above or your amendment will not be considered a complete response.

3. In the September 26, 2017 submission, you established adhesive performance tests, [redacted] (b) (4)
You have included these tests in all stability time points. However, in the September 12, 2018 submission, we cannot locate the stability results for adhesive performance test for 3 batches made with [redacted] (b) (4) [redacted] (b) (4) and for 3 batches made with [redacted] (b) (4) [redacted] (b) (4) up to 6-month time point. To compare the adhesive performance results between batches made with [redacted] (b) (4) provide all available adhesive performance test results on stability.

4. In the September 12, 2018 CR #9 response, you state that you are requesting 24-month shelf life for the drug product. However, the current document in section 3.2.P.8.1 submitted on April 14, 2016 indicates that the currently proposed expiration dating for the marketing packaging is 36 months. Clarify this discrepancy. In addition, discuss the cause for the increasing trend on the impurity at [redacted] (b) (4) at the end of shelf life and whether any changes to the control strategy are necessary to minimize formation of [redacted] (b) (4) during shelf life.

4. Labeling Deficiencies – N/A

5. Manufacturing Deficiencies – N/A

6. Biopharmaceutics Deficiencies – N/A

7. Microbiology Deficiencies – N/A

8. Pharmacology/Toxicology Deficiencies

Theme 1: Product safety
Justification 1: The drug product deficiencies have been classified as MAJOR because there is need for safety assessment of extractables and leachables, inadequate assessment of extractables and leachables, or submission of that assessment in an unsolicited amendment as noted in Appendix A, Section A(2)(o) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required for establishing safety of the drug product. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources.

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

We completed Pharmacology/Toxicology review of your information submitted in support of safety of leachables and impurities in your proposed generic lidocaine patch (5%) (dated 09/13/2018). We determined that the maximum daily exposures (b) (4) (b) (4) raise safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective. For (b) (4) you justified its general and dermal toxicity concerns using (b) (4) Such an approach is not acceptable. For (b) (4) you did not address local toxicity concern for these compounds in the context of use of your proposed product, which has dermal route of administration and can be used chronically. Therefore, your safety assessment for these compounds is inadequate and not acceptable. To address these deficiencies, we recommend the following:

- For (b) (4) address the systemic and local toxicity at its MDE level, for (b) (4) (b) (4) address the local toxicity concern at their respective MDE levels from your proposed generic product. You may provide the justification

information from published literature. The adequacy of the data from such a justification report will be a review issue upon submission.

- Alternatively, you may conduct a 90-day repeated-dose toxicity study with your final, to-be marketed formulation to qualify the safety of the above listed compounds at their potential MDE levels. Consider an appropriate animal model, clinically relevant route of administration and context of use of your generic drug product in the design of the nonclinical studies. You may provide scientific rationale for the chosen animal model and the study design. In addition, the doses used for each compound in the repeated-dose toxicity study should provide adequate margins of safety for its proposed clinical exposure from your drug product. The adequacy of the data from such nonclinical studies will be a review issue upon submission. If you have clarifying questions on the design of the nonclinical studies, you may submit your study design via General Correspondence route for our review.

Application Technical Lead Name and Date: *Brock Roughton, 01-MAY-2019*

Brock Roughton

Digitally signed by Brock Roughton
Date: 5/01/2019 10:03:36AM
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Recommendation: Complete Response - Major

ANDA 209190
Review #2

Drug Name/Dosage Form	Lidocaine Patch
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Rhodes Pharmaceuticals L.P.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
(12)	*26-SEPT-2017*	*All*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance		
Drug Product	Adchara Pongpeerapat	Brock Roughton
Process	James Norman	Yubing Tang
Microbiology	Yuansha Chen	Neal Sweeney
Facility	Cassandra Abellard	Derek Smith
Biopharmaceutics	Kelly Kitchens	Tapash Ghosh
Regulatory Business Process Manager	Camille Smith	
Application Technical Lead	Brock Roughton	
Laboratory (OTR)		
ORA Lead		
Environmental		

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

MFs:

	Type			Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	3/24/2016	Reviewed by Zhengfu Wang
	Type III		(b) (4)	N/A		
	Type II			N/A		
	Type II			N/A		
	Type IV			Adequate	11/29/2017	Reviewed by Adchara Pongpeerapat (pending upload into Panorama)
	Type IV			Inadequate	5/11/2016	Reviewed by Shalini Anand

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DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20612	RLD

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	Complete	Inadequate (link to consult response)	11/13/2017	Bella Pelina
Clinical	N/A			
Other	N/A			

Abbreviated Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Major**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Major

Lidocaine is official in USP and EP. The drug substance specification agrees with the USP monograph. The referenced DMF (b) (4) is adequate. Lidocaine exhibits one polymorphic form. The analytical methods are acceptable. The applicant should provide qualification for impurity reference standards.

Lidocaine patch 5% is non-compendial. The drug product is topical patch with a (b) (4) similar to the RLD formulation. The formulation uses (b) (4) (b) (4) (b) (4) is inadequate for (b) (4) In addition, control of adhesive impurities in the drug product is inadequate. The applicant has not adequately identified the extractables and has not adequately performed leachable studies. *This is a major deficiency. Leachables assessment is required for establishing safety of the drug product. Upon receipt, the review of this information will require substantial expenditure of FDA resources.*

The applicant has adequately mitigated the high risks identified in the initial quality risk assessment: chemical stability, physical stability (cohesive and adhesive), content uniformity and solubility. The applicant has tightened the level of (b) (4) (carcinogenic impurity) to a safe level. The proposed controls for impurities from (b) (4) are acceptable. The 36-month stability results show the increase trending in one of the unknown degradation compounds, reaching the specification limit. The applicant should justify the difference in dissolution during stability for the registration batches to assure strength, purity, and quality of the drug product during the proposed expiration dating period of 36 months.

The labeling has acceptable quality information.

B. Process: Adequate

The applicant uses a standard process for producing (b) (4) topical patches. The main process steps are (b) (4) (b) (4) The in-process controls are acceptable.

(b) (4)

C. Facility: Adequate with CDRH Deficiency

(b) (4) The last inspection of the facility was July 2016 and was classified VAI. The facility is acceptable to manufacture lidocaine for this application because of the amount of time the firm has been producing this marketed API (over 10 years), the acceptable review of the DMF, the recent inspection, and acceptable inspectional history. In addition, use of (b) (4) for testing of the drug substance is acceptable.

Altergon Italia S.r.l. (FEI# 3007086839) manufactures the drug product. The last inspection of the facility was performed November 2015 and was classified NAI. This facility is acceptable to manufacture this product because of the outcome of the inspection, the firm's acceptable compliance history, and experience with transdermal product manufacturing. In addition, use of (b) (4) (b) (4) for testing of the drug product is acceptable.

Per the CDRH consult review memo, the only manufacturing facility (Altergon) requiring review was found acceptable based on the 2016 PAI discussed above. However, the application is deficient from a documentation perspective. The CDRH deficiency will be communicated in the Complete Response letter.

D. Biopharmaceutics: Adequate

The applicant developed and validated an adequate drug release method to measure the release of lidocaine from the drug product. In addition, the firm's proposed drug release acceptance criteria are adequate based on the submitted drug release data.

The following drug release method and acceptance criteria are recommended for the test product and have been accepted by the applicant:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10 minutes: NMT (b) (4) 30 minutes: (b) (4) 180 minutes: NLT (b) (4)

E. Microbiology (if applicable): Adequate

The product is non-sterile. The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>. The applicant commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (36 months).

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None.

VIII. Microbiology Deficiencies

None.

IX. Combination Product Deficiencies

The following deficiency has been identified while conducting the documentation review of application ANDA 209190 for the Lidocaine Patch 5%, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Your response indicates that Altergon implemented an internal procedure for design control covering requirements for design and development planning, design input, design output, design review, design verification, design validation and design changes; however, reference of this procedure is not included in the response, nor is a description of Altergon's design control system provided. Further, the response did not include a summary of the plan used to design the combination product. Please provide the missing documentation.

Application Technical Lead Name and Date: I concur with the above deficiencies.

Brock Roughton, PhD, 04-DEC-2017

Brock Roughton

Digitally signed by Brock Roughton
Date: 12/08/2017 04:05:15PM
GUID: 53153a8b0000550f9c684fbc8ff833b9

QUALITY ASSESSMENT

ANDA 209190
Review 1

Drug Name/Dosage Form	Lidocaine Patch
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Rhodes Pharmaceuticals LP
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD 1 Original	*04/14/2016*	*All*
SD 3 Quality/Response to IR	*05/23/2016*	*DP, Process, Facility*
SD 7 Response to ECD/Quality	*09/29/2016*	*DP*
SD 10 Response to ECD/Quality	*01/23/2017*	*DP, Process, Facility*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance		
Drug Product	Adchara Pongpeerapat	Brock Roughton
Process	James Norman	Yubing Tang
Microbiology	Yuansha Chen	Neal Sweeney
Facility	Cassandra Abellard	Derek Smith
Biopharmaceutics	Kelly Kitchens	Haritha Mandula
Regulatory Business Process Manager	Camille Smith	
Application Technical Lead	Brock Roughton	
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

Abbreviated Executive Summary

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – Inadequate-Minor

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Minor

Lidocaine is official in USP and EP. Lidocaine exhibits one polymorphic form. The referenced DMF #011339 held by Delta Synthetic Co., Ltd. is adequate. To ensure the identity, strength, purity, and quality of the drug substance, the applicant should provide revised drug substance specification, analytical method validation, and reference standards information.

Lidocaine patch 5% is non-compendial. The drug product is topical patch with a hydrogel formulation, similar to the RLD formulation. The firm has not adequately mitigated the risks identified in the initial risk assessment (high risks: impurities, chemical stability, physical stability (cohesive and adhesive), content uniformity and solubility). The proposed specification has no control for release liner peel, cold flow, and absence of crystal. The stability results show the decrease trending in assay, but no trending in degradation compounds. The firm has not provided adequate information to demonstrate that the proposed analytical methods for drug product are fit for use.

The labeling has acceptable quality information.

B. Process: Inadequate-Minor

The applicant uses a standard process for producing hydrogel-based topical patches. The main process steps are mixing, kneading, spreading, curing, converting, and packaging. The batch size is 720-2880 kg, and no scale-up is proposed. The applicant introduced a new process line. The primary features of the new line are a faster spreading speed (10 m/min instead of 3 m/min) and faster packaging speed (300 pieces/ minute instead of 60-80 pieces/min). Microscopic patch appearance varies from batch to batch, suggesting variability in the process lines. The applicant should address the variability. The applicant should provide hold time studies for the Stage A and Stage B solutions. The applicant should define kneading and curing processes in P.3.3 or P.3.4.

C. Facility: Adequate

There are no significant outstanding issues with the firms involved in the manufacturing of the product. The CDRH consult identified several deficiencies captured in the Combination Product Deficiencies below.

D. Biopharmaceutics: Inadequate-Minor

The firm proposes to use the FDA-recommend drug release method for Lidocaine patch 5%. The drug release validation and proposed acceptance criteria are inadequate.

E. Microbiology: Inadequate-Minor

The product is non-sterile. The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>. The applicant should provide a commitment to perform preservative effectiveness test at the end of the shelf life.

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(b) (4)

perform testing as outlined in the application.

CDRH CONSULT OUTCOME:

Per the CDRH consult review memo, the only manufacturing facility (Altergon) requiring review was found acceptable based on the 2016 PAI discussed above. However, the application is deficient from a documentation perspective. The CDRH deficiencies will be communicated in the Complete Response letter. Please see consult memo uploaded with the Facility IQA Chapter for details.

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

QUALITY ASSESSMENT

List of Deficiencies:

CDRH deficiencies documented in IR#2 were not responded to by applicant in adequate time per RBPM. See CDRH consult.

Primary Facilities Reviewer Name and Date:

C. Abellard 06/12/2017 Consumer Safety Officer- OPF/ DIA-BII

Secondary Reviewer Name and Date:

D. Smith 06/26/2017

Cassandra Abellard

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Derek Smith

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MICROBIOLOGY

Product Background:

ANDA: 209190

Drug Product Name / Strength:
Proprietary: N/A
Non-proprietary: Lidocaine Patch 5%

Route of Administration: Topical patch

Applicant:
Name: Rhodes Pharmaceuticals L.P.
Address: 498 Washington Street, Coventry, Rhode Island 02816, USA

US Agent:
(b) (4)

Manufacturing Site:
Zona Industriale A.S.L.
Morra De Sanctis
Avellino 83040, Italy

Method of Sterilization: N/A. Drug product is non-sterile.

Review Summary:
The submission is **NOT** recommended for approvable on the basis of sterility assurance.

List Submissions being reviewed (table):

Submitted	Received	Date assigned to reviewer
4/14/2016	4/14/2016	2/22/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: Commitment to perform preservative effectiveness test at the end of the shelf life is not stated.

Product Quality Microbiology Assessment

All of the information in this review relates to patient risk associated with a non-sterile topical patch.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Lidocaine Patch 5% consists of a (b) (4) (b) (4) adhesive material, (b) (4) non-woven (b) (4) and covered with a (b) (4) film.

- **Drug product composition** – Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: purified water, sorbitol, glycerin, polyacrylic acid, carboxymethylcellulose sodium, propylene glycol, sodium polyacrylate, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, edetate disodium, methylparaben and propylparaben. (b) (4)

- **Description of container closure system** – N/A

Reviewer's Assessment: The drug product composition and packaging are adequately described.

ADEQUATE

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Preservative Effectiveness** – (P.5.6. (b) (4) eng.pdf)

Preservative content acceptance criteria for the drug product: 90%-110%

At the developmental phase, preservative effectiveness test was performed with (b) (4) of the labeled content of preservatives. Only test with the (b) (4) preservative content passed the acceptance criteria. Test was performed as per USP <51>. The drug product was mixed with the testing microorganisms and diluted 10X with (b) (4) resulting in 10^5-10^6 cfu/mL of inoculum. Samples were incubated 20-25°C and microorganisms were enumerated by membrane filtration method.

Acceptance criteria:
Bacteria: NLT 2 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

Log reductions w (b) (4)

Microorganisms			
S. aureus	(b) (4)		
P. aeruginosa			
E. coli			
C. albicans			
A. brasiliensis			

Reviewer's Assessment: Preservativ
topical products.

ADEQUATE

P.3 Manufacture

P.3.1 Manufacturer

Zona Industriale A.S.L.
Morra De Sanctis
Avellino 83040, Italy

This site is responsible for manufacturing, release and stability testing of the drug product.

P.3.3 Description of the Manufacturing Process and Process Controls

- **Environmental monitoring including product bioburden –**

The applicant has not provided a description of environmental monitoring or the area classifications for the commercial production of the subject drug product. However, the subject drug product is a non-sterile topical patch with a preservative and acceptable microbial limits release specification. Therefore, patient risk is low from environmental contamination.

Reviewer's Assessment: The drug product, drug product manufacturing, and process controls were sufficiently described for the reviewer to determine which data are needed for sections P.5 (Specifications) and P.8 (Stability) below.

ADEQUATE

P.5 Control of Drug Product

P.5.1 Specifications

Test	Acceptance Criteria	Method
Total Aerobic Microbial Count	(b) (4)	USP <61>
Total Yeast & Mold Count		USP <61>

S. aureus *P. aeruginosa*	(b) (4)	USP <62>

Reviewer's Assessment: The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>.

ADEQUATE

P.7 Container Closure System See section P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Proposed expiry: 36 months.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Storage condition is 25°C/60% RH. Microbial limits tests, including TAMC, TYMC, absence of *S. aureus*, and absence of *P. aeruginosa*, will be performed at initial, 6, 12, 24 and 36 month.

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Comment: Provide a statement to perform preservative effectiveness testing at the end of the drug product shelf life on at least one stability batch.

Reviewer's Assessment: The submitted post approval stability protocol and commitment does not comply with the Guidance for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products. A commitment to perform preservative effectiveness test at the end of the shelf life is requested.

INADEQUATE

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

Twenty-four months stability data were provided for lot # L1304151, L1304191 and L1304201. All microbial limits test results complied with the specification. No AET stability data was provided for the exhibit batches.

Reviewer's Assessment: ADEQUATE

R REGIONAL INFORMATION

R.1 Executed Batch Record

The batch records for exhibit batch lot # L1304151, L1304191 and L1304201 are provided.

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

A. PACKAGE INSERT

Store at 25°C; excursions permitted 15°C to 30°C. Apply lidocaine patch once up to 12 hours within a 24 hour period.

Reviewer's Assessment: There are no product quality microbiology issues related to drug product administration instructions described in the package insert.

ADEQUATE

List of deficiencies:

The following deficiencies listed below are: ☐ **Major** ☒ **Minor**
Major deficiencies - A CR is recommended ☐
Minor deficiencies - ☒ **10 day ECD** ☐ **30 day IR**

Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (reference: *Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products - Questions and Answers*).

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.

CDER/OPQ/OPF/DMA

4/21/2017

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

Neal J. Sweeney, Ph.D.

CDER/OPQ/OPF/DMA

4/21/2017

Yuansha Chen

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Neal Sweeney

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

BIO PHARM /TOX REVIEW(s)

PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Product:	Lidocaine patch (5%)
ANDA#: **Applicant:**	209190 Rhodes Pharmaceuticals LP.
RLD#/Approval Date: **Sponsor:**	NDA 20612 (Lidoderm®; Lidocaine Patch, 5%); Approved on 03/19/1999 Teikoku Pharma USA Inc.
Pharmacology-Toxicology Primary Reviewer:	Narendranath Reddy Chintagari, BVSc & AH, MVSc, PhD Pharmacologist, DCR
Pharmacology-Toxicology Secondary Reviewer:	Sree Rayavarapu, DVM, PhD Staff Fellow (Toxicologist), DCR
Tertiary Reviewer:	Daiva Shetty, MD Acting Division Director, DCR
To:	Adchara Pongpeerapat, PhD Chemist, Division of Modified Release Products (DMRP), Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To evaluate the applicant's response (Amendment-14; submitted on 07/30/2019) to FDA-Complete Response Letter (CRL; dated 05/03/2019). Specifically, to review the safety of (b) (4)
Date of FDA-Complete Response:	05/03/2019
Date Response to FDA-Complete Response:	07/30/2019
Date of Completion:	11/07/2019
Conclusion:	• Fo (b) (4) the applicant provided comparative analytical data which demonstrated that (b) (4) from the proposed generic lidocaine when compared to Reference Listed Drug (RLD). DCR-Pharmacology/Toxicology defers the review and acceptability of comparative analytical data to Quality discipline. DCR-Pharmacology/Toxicology does not have any further deficiencies related to TMS. • Fo (b) (4) the proposed maximum daily exposure (MDE) levels are not likely to be different than that of RLD. Thus, the proposed do not raise any safety concern from a Pharmacology/Toxicology perspective. See Section 2 for Internal Recommendations. There is nothing to be conveyed to the ANDA applicant.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 Executive Summary:

This DCR Pharmacology/Toxicology (DCR-P/T) review evaluates ANDA 209190 applicant's response to FDA-Complete Response letter (CRL; Dated 05/03/2019). Specifically, this review [redacted]

The reference listed drug (RLD) is Lidoderm® (Lidocaine patch 5%; NDA 020612). The RLD is indicated for relief of pain associated with post-herpetic neuralgia. The maximum daily dose of lidocaine patch (5%) is 3 patches/day.

In the previous review cycle (review dated 04/29/2019), DCR-P/T reviewed the safety o [redacted] leachables [redacted] and [redacted] impurities [redacted] DCR- P/T concluded that the maximum daily exposures (MDEs) to [redacted] were determined not acceptable as there are inadequate data to justify their local and systemic toxicity concerns. P/T recommendations were conveyed to the ANDA applicant in a Complete Response (CR) letter dated 05/03/2019. The applicant responded to the CR on 07/30/2019 (Amendment-14).

Fo [redacted] the applicant provided comparative analytical data and demonstrated tha [redacted] leaches at [redacted] level from the proposed generic lidocaine when compared to RLD. The amount of [redacted] varied from [redacted] in RLD an [redacted] in the proposed generic lidocaine. The review and acceptability of analytical data is deferred to the Quality discipline. Nevertheless, based on the levels o [redacted] reported, its MDE is likely to be lower from the generic lidocaine when compared to RLD. Thus, the MDE o [redacted] from the proposed generic does not raise any safety concern when compared to RLD. Thus, DCR-P/T does not have any further deficiencies related t [redacted]

[redacted] Thus, it is likely that human subjects will be exposed to same levels of [redacted] and [redacted] if proposed generic is taken in place of RLD. Furthermore, DCR Clinical team reviewed Clinical trial data and did not identify any sensitization and irritation risk potential for the proposed generic lidocaine drug product. Thus, DCR-P/T determined that the proposed level [redacted] are not likely to alter the safety profile of generic lidocaine when compared to the RLD.

In summary, there are no further deficiencies related to [redacted] and the proposed levels o [redacted] do not raise any safety concerns from a P/T perspective.

2 Internal Recommendation:

Fo [redacted] the applicant did not provide any new nonclinical data. However, the applicant provided comparative analytical data which demonstrated tha [redacted] leaches at [redacted] level from

the proposed generic lidocaine when compared to Reference Listed Drug (RLD). DCR-P/T defers the review and acceptability of analytical data to Quality discipline. DCR-P/T does not have any further deficiencies related t (b) (4)

Fo (b) (4) the proposed maximum daily exposure (MDE) levels are not likely to be different than that of RLD. Thus, the proposed levels do not raise any safety concern from a P/T perspective.

3 External Recommendation:

There are no recommendations to the applicant.

4 Regulatory Background:

Rhodes Pharmaceuticals submitted ANDA 209190 for generic lidocaine patch on 04/14/2016.[1] OPQ sent a CR letter (dated 12/19/2017) and advised that the applicant to justify the safety of the leachables with MD (b) (4) in their proposed generic lidocaine.[2] In addition, OPQ recommended the applicant to tighten specification limits o (b) (4) to threshold for toxicological concern or justify their safety at proposed daily exposure levels.

The applicant responded to the CRL on 09/12/2018 and submitted a safety justification for (b) (4)

In this regard, OPQ consulted (dated 10/25/2018) DCR-P/T to evaluate the safety of the leachables and impurities identified in the proposed generic lidocaine patch.[5] DCR-P/T completed first cycle review (dated 04/29/2019) and determined that the levels o (b) (4) an (b) (4) were acceptable but the levels o (b) (4) were determined to be not acceptable.[6] P/T deficiencies were communicated to the applicant in a CR letter (dated 05/03/20119).[7] The applicant responded to the CR and submitted a justification for

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[1] ANDA 209190; Lidocaine patch (5%); DARRTS; Application history https://darrts.fda.gov/darrts/faces/ApplicationHistoryContent/viewApplicationHistoryContent?_afrRedirect=5305837051999957&_afrPage=3

[2] ANDA 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 1.11.1. Quality Information Amendment \\cdsesub1\evsprod\anda209190\0011\m1\us\111-information-amendment\quality-information-amendment\fda-crl-dated-19-dec-2017.pdf

[3] ANDA 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 1.11.1. Quality Information Amendment \\cdsesub1\evsprod\anda209190\0011\m1\us\111-information-amendment\quality-information-amendment\response-to-crl-9-11-2018.pdf

[4] ANDA 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 3.2. P.7. Container Closure System \\cdsesub1\evsprod\anda209190\0011\m3\32-body-data\32p-drug-prod\lidocaine-patch-topical-altergon\32p7-cont-closure-sys\container-closure-system-13.pdf

[5] ANDA 209190; Lidocaine patch; Panorama; Application Lifecycle; Send consult request (Dated 10/25/2018) http://panorama.fda.gov/document/view?ID=5bd1a4c900b1abfba3bfd14d5c1090f3

[6] ANDA 209190; Lidocaine patch; Panorama; Application Lifecycle; Respond to consult request (dated 04/19/2019) http://panorama.fda.gov/document/preview?versionID=5ccc37d100243eeffa7139ade7d12d7b&ID=5cc725720042f3af633a9f780c0763cb

[7] ANDA 209190; Lidocaine patch; Panorama; Application Lifecycle; Upload final decision (dated 05/03/2019) http://panorama.fda.gov/document/preview?versionID=5ccc2eec0022f41e9f0588b9d0eecd65&ID=5ccade87000758794a38398399c08309

the safety o [redacted] (Amendment-14, dated 07/30/2019).[8] The applicant submitted justification related to P/T deficiencies is the subject of this review.

5 Discussion

In current post-CR Amendment-14 (dated 07/30/2019), the applicant submitted information to justify the safety of [redacted] in the generic lidocaine patch. The safety of proposed levels of [redacted] are discussed below.

Evaluation of safety o [redacted]

During the first cycle review, DCR-P/T evaluated the safety o [redacted] at a daily exposure level of [redacted] in the proposed generic lidocaine patch. DCR-P/T determined that the exposure [redacted] raises safety concern due to inadequate systemic and local toxicity data.

In the current post-CR submission (Amendment-14), the applicant provided nonclinical data from published literature to justify the safety o [redacted] In addition, the applicant also provided comparative analytical data to show the levels o [redacted] that can potentially leach from RLD vs proposed generic lidocaine.

DCR-P/T reviewed majority of the nonclinical submitted by the applicant in the previous review cycle. Applicant's current submission did not provide any additional nonclinical data that can alter previous P/T determination. Nevertheless, the applicant provided comparative analytical data to show the level o [redacted] that can potentially leach from RLD vs proposed generic lidocaine. Th [redacted] levels were measured at 32°C and 42°C a [redacted] different p [redacted] conditions. Comparative analytical data indicate tha [redacted] leached a [redacted] level from proposed generic (in the range o [redacted] compared to RLD (in the range of [redacted] The amounts o [redacted] leached from RLD and proposed generic under different tested conditions are shown in Table 1 below.

[redacted]

The review and acceptability of analytical data is deferred to the Quality discipline. Based on the levels o [redacted] observed in RLD vs proposed generic, the MDE o [redacted] is likely to b [redacted] from the proposed generic lidocaine when compared to RLD. Thus, the level o [redacted] from the proposed generic does not raise any safety concern. DCR-P/T does not have any further deficiencies related t [redacted]

[8] ANDA 209190; Lidocaine patch; GS Review; Sequence 0012(14); Dated 07/30/2019; Module; 1.11.4. Multiple Module Information Amendment (dated 07/30/2019) \\cdsesub1\evsprod\anda209190\0012\m1\us\111-information-amendment\multiple-module-information-amendments\response-crl-0012.pdf

Evaluation of safety of (b) (4):

In the previous cycle, DCR-P/T concluded that proposed levels o (b) (4) raises local toxicity concern. Therefore, DCR-P/T recommended that the applicant to justify the local toxicity of (b) (4) at their proposed levels.

In the current post-CR Amendment-14, the applicant did not provide any new toxicology information fo (b) (4); however, applicant provided summary of results a dermal exposure study (exposure dose-1%; duration-3 times/week; lifetime) conducted in mice to justify the levels o (b) (4) DCR-P/T reviewed this dermal toxicity study in the previous cycle and concluded that this study does not adequately justify the local toxicity of proposed level of (b) (4)

Fo (b) (4) the applicant did not provide any new toxicology information to justify the proposed levels. However, the applicant tried to justify the levels by indicating that polyacrylic acid constitutes only (b) (4) of formulation weight of lidocaine patch and thus, the level of (b) (4) is (b) (4) which does not raise safety concern based on existing data. We have previously reviewed available local and systemic toxicity data fo (b) (4) and concluded that MDE of (b) (4) from proposed generic are not justified.

(b) (4) Based on this information, it is likely that human subjects will be exposed to same levels of (b) (4) (b) (4) if proposed generic lidocaine is taken in place of RLD.

The applicant claimed that amounts of (b) (4) are likely to be (b) (4) in the final drug product as these compounds wer (b) (4) analytical evaluation threshold (AET) o (b) (4) in the leachable studies. Generally, leachable studies are not used to qualify exposures to impurities from the excipients; however, these data suggest that the levels of (b) (4) are likely to be (b) (4) in the final drug product.

Furthermore, DCR Clinical team reviewed Clinical trial data and did not identify any sensitization and irritation risk potential for the proposed generic lidocaine drug product.[10]

Thus, DCR-P/T determined that the proposed level (b) (4) are not likely to alter the safety profile of generic lidocaine when compared to the RLD.

[9] ANDA 209190; Lidocaine Patch; Mercado; Drug Product Primary Review; Dated 06/01/2017 http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88128bf9f

[10] ANDA 209190; Lidocaine patch; Panorama; Application Lifecycle; Clinical Primary Review; Dated 06/19/2017 http://panorama.fda.gov/document/preview?versionID=59481e4600986e05dca721a57963dd8a&ID=59480aac0096c6f4ae1f00967866a170

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(b) (4)

6 Conclusion:

Fo (b) (4) the applicant provided comparative analytical data which demonstrated tha (b) (4) leac at a lower level from the proposed generic lidocaine when compared to RLD. DCR-P/T defers the review and acceptability of comparative analytical data to Quality discipline. DCR-P/T does not have any further deficiencies related t (b) (4)

Fo (b) (4) the proposed MDE levels are not likely to be different than that of RLD. Thus, the proposed do not raise any safety concern from a P/T perspective.

See Section 2 for Internal Recommendations.

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[11] ANDA 209190; GS Review; Sequence 0011(13); Dated 09/12/2018; Module 3.2. P.4.1. Specifications; Polyacrylic acid \\cdsesub1\evsprod\anda209190\0011\m3\32-body-data\32p-drug-prod\lidocaine-patch-topical-altergon\32p4-contr-excip\polyacrylic-acid\specifications-1.pdf

[12] ANDA 209190; GS Review; Sequence 0011(13); Dated 09/12/2018; Module 3.2. P.4.1. Specifications; Sodium Polyacrylate \\cdsesub1\evsprod\anda209190\0011\m3\32-body-data\32p-drug-prod\lidocaine-patch-topical-altergon\32p4-contr-excip\sodium-polyacrylate\specifications-1.pdf

[13] NDA 20612; Lidoderm® (Lidocaine); GS Review; Sequence 0009(670); Dated 05/03/2019; Module 1.13.5. Summary of manufacturing changes \\cdsesub1\evsprod\nda020612\0009\m1\us\113-ann-rep\sum-manu-chan.pdf (Page #12)

Narendranath Reddy Chintagari

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Sree Rayavarapu

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Daiva Shetty

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PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)
Lidocaine Patch 5%

Drug Product:	Lidocaine Patch 5%
DMF#/ANDA#: **Applicant:**	ANDA 209190 Rhodes Pharmaceuticals LP
RLD#/Approval Date: **Sponsor:**	NDA 20612, Approved 03/19/1999 Teikoku Pharma USA Inc
Pharmacology-Toxicology Primary Reviewer:	Wei Ding, PhD, DABT Toxicology reviewer, DCR
Pharmacology-Toxicology Secondary Reviewer:	Victoria Keck, MS, VMD Toxicologist, DCR
Tertiary Reviewer:	Daiva Shetty, MD Acting Director, DCR
To:	Adchara Pongpeerapat, Ph.D. Division of Modified Release Products (DMRP) Office of Lifecycle Drug Products (OLDP) Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To review Ames assay results o [redacted] (b) (4)
Date of Submission:	08/08/2019
Date Consult Received:	08/20/2019
Date of Completion:	09/18/2019
Conclusion:	Under the conditions of the valid Ames assay, the impurit [redacted] (b) (4) did not exhibit bacterial mutagenicity potential and can be controlled as a non-mutagenic impurity.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1. Executive Summary:

This Pharmacology/Toxicology review addresses a consult request from the Division of Modified Release Products (DMRP), in the Office of Pharmaceutical Quality (OPQ) to review Ames test for the impurity [redacted] (b) (4) in Lidocaine Patch 5% under ANDA 209190.

The reference listed drug (RLD) for Lidocaine Patch 5% is Lidoderm® (Lidocaine Patch 5%) under NDA 20612. The RLD was approved on 03/19/1999 and it is sponsored by Teikoku Pharma USA Inc. Lidoderm (Lidocaine Patch 5%) is comprised of an adhesive material containing 5% lidocaine. The size of the patch is 10 cm x 14 cm. Lidoderm® is indicated for relief of pain associated with post-herpetic neuralgia, which should be applied only to intact skin.[1] The maximum daily dose (MDD) is 2100 mg of lidocaine or 3 patches/day. If controlled the impurity level as not more than (NMT [redacted] (b) (4) the limit of impurity is NMT [redacted] (b) (4) or [redacted] (b) (4)

Based on computational mutagenicity analysis (report # TSI-18-001), Rhodes Pharmaceuticals LP, the ANDA applicant, states that the impurit [redacted] (b) (4) is potentially mutagenic. To justify the proposed limit of NMT [redacted] (b) (4), the applicant submitted an Ames test of the impurity and concluded that the impurity is non-mutagenic. OPQ consulted DCR to evaluate the Ames test result and assess the mutagenicity potential of [redacted] (b) (4)

Upon review, DCR Pharm/Tox determined that under the conditions of the conducted Ames test, [redacted] (b) (4) is not mutagenic in any of the tested four *Salmonella* strains (TA98, TA100, TA1535, TA1537) and *Escherichia coli* strain WP2 uvrA both in the presence and absence of metabolic activation (S9).

2. Recommendation (Internal)

Under the conditions of this valid Ames assay [redacted] (b) (4) is not mutagenic and may be controlled as a non-m

3. Comments to be conveyed by the RPM to the ANDA applicant:

N/A.

4. Regulatory Background:

Rhodes Pharmaceuticals LP submitted ANDA 209190 for Lidocaine Patch 5%. The RLD for Lidocaine Patch 5% is Lidoderm® (Lidocaine Patch 5%) under NDA 20612. The RLD was approved on 03/19/1999 and it is sponsored by Teikoku Pharma USA Inc.

[1] RLD (NDA 020612, Lidoderm®) Drug Label Information obtained at Drugs@fda: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020612s014lbl.pdf Accessed at: 08/26/2019

The (Q)SAR study of the impurit [redacted] indicated that it is potentially mutagenic. To justify a limit that exceeds the Threshold of Toxicological Concern (TTC), the ANDA applicant submitted the Ames test report to justif [redacted] as non-genotoxic impurity.[2] DMRP/OLDP consulted DCR (dated 08/08/2019) to evaluate the Ames assay results and assess the mutagenicity potential of th [redacted] impurity.

5. Genetic Toxicology:

Study title:	Bacterial Reverse Mutation Assay
Study number:	[redacted]
Study report location:	[redacted]
Submission time:	7/11/2019
Study Sponsor:	[redacted]
Conducting laboratory:	
Date of study initiation:	2/11/2019
GLP compliance:	Yes
QA statement:	Yes
Test article:	[redacted]
Test article description:	
Batch #:	
Purity:	

5.1. Key Findings:

[redacted] did not induce a dose-dependent increase of the revertant colonies in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and in *Escherichia coli* strain WP2*uvr*A, both in presence and absence of metabolic activation (S9). Under the conditions of this valid Ames assa [redacted] is not mutagenic.

[2] ANDA 209190, Ames report in 3.3.P.2, at \\cdsesub1\evsprod\anda209190\0012\m3\32-body-data\32p-drug-prod\lidocaine-patch-topical-altergon\32p2-pharm-dev\pharmaceutical-development-3.pdf Accessed 08/26/2019

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5.5. Study Validity:

The submitted Ames assay is valid because of the following reasons:

- The selection of four strains of *Salmonella typhimurium* and one strain of *E. coli* is adequate and is in accordance with OECD 471 guideline.
- The specification and concentration of S (b) (4) is within acceptable range.
- The dose selection is adequate based on th he limit dos (b) (4) and dose selections were within half log intervals.
- At least three nontoxic doses are tested using each strain both in presence and absence of S9.
- Background mutants per plate are within the historical range for each bacterial strain both in presence and absence of S9.
- Positive controls produced clear increase in the mean number of revertant colonies per plate when compared to vehicle control.
- Use o (b) (4) as the sole positive control in the presence of S9 is acceptable because the efficacy of S9 mix was characterized using an additional mutagen, (b) (4) which requires metabolic activation

6. Discussion:

(b) (4) did not produce a dose-dependent increase in the mean number of revertants, in any of the five tester strains, at the top doses tested both in the absence and the presence of S9. The negative control and positive control values all fall into the historical control value range. The positive controls used in the current study produced more than 3-fold increase in the mean number of revertants in all the five tester strains, in the absence as well as in presence of S9. Hence, under the conditions of this valid Ames assa (b) (4) (b) (4) is not mutagenic.

7. Conclusion:

Under the conditions of the valid Ames assay, impurity (b) (4) did not exhibit bacterial mutagenicity potential.

Wei Ding

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Victoria Keck

Digitally signed by Victoria Keck
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Daiva Shetty

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Date: 9/18/2019 01:43:39PM
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PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Lidocaine patch (5%)

Drug Product:	Lidocaine patch (5%)
ANDA#: **Applicant:**	209190 Rhodes Pharmaceuticals LP.
RLD#/Approval Date: **Sponsor:**	NDA 20612 (Lidoderm®; Lidocaine Patch, 5%); Approved on 03/19/1999 Teikoku Pharma USA Inc.
Pharmacology-Toxicology Primary Reviewer:	Narendranath Reddy Chintagari, BVSc &AH, MVSc, PhD Pharmacologist, DCR
Pharmacology-Toxicology Secondary Reviewer:	Sree Rayavarapu, DVM, PhD Staff Fellow (Toxicologist), DCR
Tertiary Reviewer:	Mark Ritter, MD Associate Director, DCR
To:	Adchara Pongpeerapat, PhD Chemist, Division of Modified Release Products (DMRP), Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To evaluate the safety and acceptability o (b) (4) leachables (b) (4) in the generic lidocaine patch.
Date of Submission:	09/12/2018
Date Consult Received:	10/02/2018
Date of Completion:	04/29/2019
Conclusion:	The MDE (b) (4) pose safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective. See Section 2 for Internal Recommendations and Section 3 for Comments to be conveyed to the ANDA Applicant by the RPM.
Deficiency Classification:	☒ Major ☐ Minor ☐ N/A (Review is Adequate)

Extractables/Leachables review: The deficiency requires justification or nonclinical studies that support the safety of the proposed drug product. As described in Appendix A of the *Guidance for Industry ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018),* the need for a safety assessment of impurities, extractables and leachables, or inadequate assessment of impurities, extractables and leachables is classified as a major deficiency. Review of the submitted justification or toxicology data will require substantial expenditure of FDA resources.

1 Executive Summary:

This Pharmacology/Toxicology review address a consult request from the Division of Modified Release Products (DMRP) in the office of Pharmaceutical Quality (OPQ) to evaluate the safety o (b) (4) leachable (b) (4) an (b) (4) impuritie (b) (4) in the proposed generic lidocaine patch (ANDA 209190).

Rhodes Pharmaceuticals submitted ANDA 209190 for generic lidocaine patch. The Reference Listed Drug (RLD) is Lidoderm® (lidocaine), NDA 020612. Lidocaine patch is indicated for relief of pain associated with post-herpetic neuralgia. The maximum daily dose (MDD) of lidocaine is 3 patches per day. Rhodes Pharmaceuticals performed analytical studies to identify potential leachables in their proposed generic lidocaine product. The applicant set an Analytical Evaluation Threshold (AET) limit o (b) (4) The applicant's analytical methods are acceptable from a Quality perspective. The applicant's AET is acceptable from a Pharmacology/Toxicology perspective.

The safety and acceptability of each of th (b) (4) leachable (b) (4) an (b) (4) impuritie (b) (4) in the proposed generic lidocaine patch is discussed below.

(b) (4)

(b) (4)

2 Internal Recommendation:

The maximum daily exposure (MDE) levels o (b) (4) (b) (4) do not pose any safety concern and thu (b) (4)

[1] Erucamide, 21CFR § 175.105
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=175.105

[redacted] pose a safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective.

Recommendations to be conveyed to the ANDA applicant are provided in Section 3 below.

DCR has identified MAJOR deficiencies to be included in the Complete Response Letter. The comments in Section 3 must conveyed to the ANDA applicant AS WRITTEN under the "PHARMACOLOGY/TOXICOLOGY" section of the Complete Response Letter. DCR considers these deficiencies to be MAJOR deficiencies to be included in the Complete Response Letter. These must NOT be communicated to the Applicant in an Information Request. Please notify DCR when the applicant responds to this deficiency.

3 Comments to be conveyed by the RPM to the ANDA applicant as written:

INADEQUATE OUTCOME -THE RESPONSE NEEDS TO BE REVIEWED BY DCR

DCR has identified MAJOR deficiencies to be included in the Complete Response Letter. The comments in Section 3 must conveyed to the ANDA applicant AS WRITTEN under the "PHARMACOLOGY/TOXICOLOGY" section of the Complete Response Letter. DCR considers these deficiencies to be MAJOR deficiencies to be included in the Complete Response Letter. These must NOT be communicated to the Applicant in an Information Request. Please notify DCR when the applicant responds to this deficiency.

We completed Pharmacology/Toxicology review of your information submitted in support of safety of leachables and impurities in your proposed generic lidocaine patch (5%) (dated 09/13/2018). We determined that the maximum daily exposures (MDEs) levels of [redacted] raise safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective.

Fo [redacted] you justified its general and dermal toxicity concerns usin [redacted] approach. Such an approach is not acceptable. Fo [redacted] you did not address local toxicity concern for these compounds in the context of use of your proposed product, which has dermal route of administration and can be used chronically. Therefore, your safety assessment for these compounds is inadequate and not acceptable. To address these deficiencies, we recommend the following:

- Fo [redacted] address the systemic and local toxicity at its MDE level, for [redacted] address the local toxicity concern at their respective MDE levels from your proposed generic product. You may provide the justification information from published literature. The adequacy of the data from such a justification report will be a review issue upon submission.
- Alternatively, you may conduct a 90-day repeated-dose toxicity study with your final, to-be-marketed formulation to qualify the safety of the above listed compounds at their potential MDE levels. Consider an appropriate animal model, clinically relevant route of administration and context of use of your generic drug product in the design of the nonclinical studies. You may provide scientific rationale for the chosen animal model and the study design. In addition, the doses used for each compound in the repeated-dose toxicity

study should provide adequate margins of safety for its proposed clinical exposure from your drug product. The adequacy of the data from such nonclinical studies will be a review issue upon submission. If you have clarifying questions on the design of the nonclinical studies, you may submit your study design via General Correspondence route for our review.

4 Regulatory Background:

On 04/14/2016, Rhodes Pharmaceuticals LP submitted ANDA 209190 for generic lidocaine patch.[2] In a Complete Response Letter (CRL) (dated 12/19/2017), FDA advised the applicant to justify safety of the leachables with MD (b) (4) in their proposed generic drug product.[3] FDA also recommended that applicant sh specification limits o (b) (4) to threshold for toxicological concern or justify MDE to (b) (4) (b) (4) The applicant responded to the CRL on 09/12/2018. In CR response, the applicant submitted a safety justification for leachable (b) (4) (b) (4) an (b) (4) impuritie (b) (4) in their proposed generic lidocaine patch.[4,5] In this rega roducts (DMRP) in the OPQ consulted DCR Pharmacology/Toxicology to evaluate the safety of the leachable (b) (4) (b) (4) and impuritie (b) (4) identified in the ocaine patch (da bmitted information is the subject of this review.

4.1 Orange Book Information

There are 3 marketed entries in the Orange Book for Lidocaine patch (5%) (Table 1).

Table 1: Orange Book Listed Lidocaine 5% Products (n= 3).

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020612	AB	Yes	Lidocaine	Patch; Topical	5%	Lidoderm	Teikoku Pharma USA.
A200675	AB	No	Lidocaine	Patch; Topical	5%	Lidocaine	Actavis Labs UT Inc.
A202346	AB	No	Lidocaine	Patch; Topical	5%	Lidocaine	Mylan Technologies Inc.

Source: Search on 01/29/2019 by this reviewer of the Orange Book, website: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process;
TE=Therapeutic Equivalence
RLD=Reference Listed Drug

[2] ANDA 209190; Lidocaine patch (5%); DARRTS; Application history https://darrts.fda.gov/darrts/faces/ApplicationHistoryContent/viewApplicationHistoryContent?_afrRedirect=5305837051999957&_afrPage=3

[3] ANDA 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 1.11.1. Quality Information Amendment \\cdsesub1\evsprod\anda209190\0011\m1\us\111-information-amendment\quality-information-amendment\fda-crl-dated-19-dec-2017.pdf

[4] ANDA 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 1.11.1. Quality Information Amendment \\cdsesub1\evsprod\anda209190\0011\m1\us\111-information-amendment\quality-information-amendment\response-to-crl-9-11-2018.pdf

[5] 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 3.2.P.7. Container Closure System \\cdsesub1\evsprod\anda209190\0011\m3\32-body-data\32p-drug-prod\lidocaine-patch-topical-altergon\32p7-cont-closure-sys\container-closure-system-13.pdf

5 Labeling

The current labelling for Lidoderm® [lidocaine patch (5%)] was approved on 11/02/2018. There is no boxed warning.[6]

5.1 Indications

Lidoderm® is indicated for relief of pain associated with post-herpetic neuralgia.[6]

5.2 Dosage and Administration

According to RLD labeling, Lidoderm® should be applied to intact skin to cover the most painful area. Prescribed number of patches (maximum of 3), should be applied only once for up to 12 hours within a 24-hour period.[6]

6 Discussion

The Division of Modified Release Products (DMRP), OPQ, requested DCR-P/T to review safety o (b) (4) leachable (b) (4) and (b) (4) impuritie (b) (4) (b) (4) in generic lidocaine patch (ANDA 209190). The applicant submitted safety justification for leachables and impurities using the information from the Cosmetic Ingredient Review (2014), Norwegian Food Safety Authority (NFSA), European Food Safety Authority (EFSA), European Chemicals Agency (ECHA) and Joint FAO/WHO Expert Committee on Food Additives (JECFA) and published literature.[5]

The maximum daily exposure (MDE) levels of each of the compounds at the maximum daily dose (MDD: 3 patches/day) of the proposed generic lidocaine are listed in Table 2 below.

Table 2: Maximum daily exposure (MDE) of leachables and impurities under review in the current consult.

(b) (4)

The safety of each of th (b) (4) leachables and th (b) (4) impurities in the proposed generic lidocaine patch is discussed below.

Evaluation of safety o (b) (4)
(Acceptable):

Toxicological evaluation fo (b) (4) was based on the information from the CIR, 2014.[7] The applicant indicated that rmation o (b) (4) was not available. Howeve (b) (4)

[6] NDA 020612; Lidoderm; Drugs@FDA: FDA Approved Drug Products https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020612

(b) (4)

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(b) (4)

7 Conclusion:

The maximum daily exposures (MDEs) o (b) (4) and (b) (4) do not raise any safety concern from a Pharmacology/Toxicology p er, the applicant did not provide adequate information to justify the safety of MDE of (b) (4) The MDE level o (b) (4) in proposed generic lidocaine raises safety concern. Thus, MDE o (b) (4) (b) (4) is not accep

(b) (4)

http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88175f9f2

Narendranath Reddy Chintagari

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Sree Rayavarapu

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Mark Ritter

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	209190	
Drug Product Name	Lidocaine Patch	
Strength(s)	5%	
Applicant Name	Rhodes Pharmaceuticals L.P.	
Applicant Address	498 Washington Street, Coventry, Rhode Island 02816, USA	
US Contact Name and US Mailing Address	Todd M. Delehant, Ph.D., Director Regulatory Affairs 498 Washington Street, Coventry, Rhode Island 02816, USA todd.delehant@pharma.com	
US Contact Telephone Number	401-262-9425	
US Contact Fax Number	401-262-9450	
Original Submission Date(s)	04/14/2016	
Submission Date(s) of Amendment(s) Under Review	Response to ECD/Bioequivalence on 08/05/2016 (SD-4)	
Primary Reviewer	Yibo Wang, Ph.D.	
Secondary Reviewer	Jennifer N. Miller, Ph.D.	
Tertiary Reviewer	N/A	
Study Number(s)	**RP-LID-PK001**	RP-LID-SSI
Study Type(s)	**Fasting**	Skin irritation/sensitization/adhesion studies
Strength(s)	5%	
Clinical Site	Frontage Clinical Services, Frontage Laboratories, Inc.	
Clinical Site Address	241 Main Street, Hackensack, New Jersey 07601 Tel: 201-678-0288; Fax: 201-342-3413	
Analytical Site	(b) (4)	
Analytical Site Address		
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** **☐ Pending** **☐ Complete** **☐ N/A (Waiver)**	**Post October 1, 2014 ANDAs** **☐ To Be Determined by OSIS** **☐ Pending For Cause Inspection** **☒ Complete**
Waiver	**☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A**	
QC Dissolution	**☐ Pending ☐ Adequate ☒ Inadequate**	
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**		
Deficiency Classification	☐ **Major (Deficiencies to be communicated by CR)** ☐ **Minor** ☒ **N/A (Review is Adequate)**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1, 3, 4	**Fasting**	**5%**	☒ **Adequate** ☐ **Inadequate**

1 EXECUTIVE SUMMARY

This application contains the results of three studies, (1) a pharmacokinetic (PK) endpoint bioequivalence (BE) study (#RP-LID-PK001), comparing the test product, Rhodes Pharmaceuticals L.P.'s Lidocaine Patch, 5%, to the corresponding reference product, Teikoku Pharma USA's Lidoderm® (lidocaine) Patch, 5% under fasting conditions; (2) an adhesion study (#RP-LID-SSI); and (3) a skin irritation and sensitization study (#RP-LID-SSI). The Division of Bioequivalence (DB) II will review the BE study and the Division of Clinical Review (DCR) will review the adhesion study and irritation/sensitization study.

The BE study was designed as a single-dose, two-way crossover study in healthy male and female subjects, in which residue in the patches was also assayed for "apparent dose" as per the Product-Specific Guidance for Lidocaine Patch.[1] The firm's fasting BE study is acceptable. The results are summarized in the table below.

Lidocaine Patch 5%, Dose (3 x 700 mg) Fasting Bioequivalence Study No. RP-LID-PK001, N=39 (Male=18 and Female=21) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng·hr/mL	(b) (4)			
AUC∞ (ng·hr/mL				
Cmax (ng/mL				

There is no USP dissolution method, but there is a FDA-recommended dissolution method for this drug product. The firm conducted dissolution testing using the FDA-recommended method [500 mL of Acetic Acid/Sodium Acetate Buffer, pH 4.0 at 32°C,

[1] Product-Specific Guidance for Lidocaine Patch (Recommended Dec 2006; Revised May 2007, July 2014, Jan 2016, Oct 2016)

with USP Apparatus V (Paddle over Disk) at 50 rpm]. The firm's QC dissolution method and data were reviewed separately and found inadequate.[2]

No Office of Study Integrity and Surveillance (OSIS) inspection is pending or necessary.

The application is acceptable with no deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[3]

Test Product	Lidocaine Patch, 5%
Reference Product	Lidoderm® (lidocaine) Topical Patch, 5%

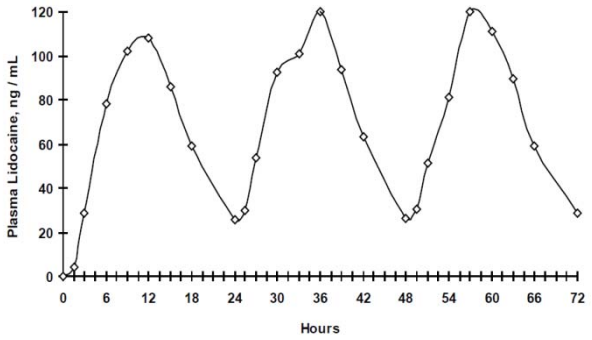
[2] GDRP, ANDA-209190-ORIG-1, Biopharmaceutics Quality Review, ANDA 209190 Biopharm.docx, dated 2/23/2017.
[3] Online Orange Book, search: lidocaine/patch, accessed on 07/15/2016. http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020612&TABLE1=OB_Rx

RLD Manufacturer	Teikoku Pharma USA
NDA No.	020612
RLD Approval Date	March 19, 1999

3.2 PK/PD Information[4]

Most recent RLD label (provide embedded document) Please check if an NG tube study is needed.	Lidoderm label_01072015.pdf
Indication	LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin.
Boxed warning	N/A
Bioavailability	The amount of lidocaine systemically absorbed from LIDODERM is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three LIDODERM patches were applied over an area of 420 cm^2 of intact skin on the back of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. **Table 1** Absorption of lidocaine from LIDODERM Normal volunteers (n= 15, 12-hour wearing time) LIDODERM Patch: 3 patches (2100 mg); Application Site: Back; Area (cm^2): 420; Dose Absorbed (mg): 64 ± 32; C_{max} (µg/mL): 0.13 ± 0.06; T_{max} (hr): 11 hr When LIDODERM is used according to the recommended dosing instructions, only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 µg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for three days, indicated that the lidocaine concentration does not increase with daily use. The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1. **Figure 1** Mean lidocaine blood concentrations after three

[4] Drugs@FDA, search: Lidoderm, accessed on 07/15/2016, label approved on 01/07/2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020612s012lbl.pdf

	consecutive daily applications of three LIDODERM patches simultaneously for 12 hours per day in healthy volunteers (n = 15). 
Food Effect	The RLD label does not mention food effect.
Tmax	11 hours
Metabolism	It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM (lidocaine patch 5%). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.
Excretion	Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 SD, n = 15).
Half-life	The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15).
Maximum Daily Dose	Three patches simultaneously for 12 hours
Handling and Disposal	Hands should be washed after the handling of LIDODERM, and eye contact with LIDODERM should be avoided. Do not store patch outside the sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them. LIDODERM should be kept out of the reach of children.

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	The guidance was revised per OGD Science Staff Review (July 2014 version): V:\Science Group\Master Files BE Posting\Lidocaine_toppatch_20612\ Lidocaine_toppatch_20612_RV06-14.pdf The Guidance was revised under Project #661508, Lidocaine topical patch, 5%, RLD 020612 BE Guidance Finalization, BE Guidance Revision lidocaine patch 20612.pdf, dated 12/8/2015 (Jan 2016 version). http://panorama.fda.gov/project/view?ID=5579b91e0081e7894828f83417e7ece3 The Guidance was further revised under Project #9045599, Lidocaine Topical Patch RLD 020612 Revised Draft BE Guidance, 9045599 Lidocaine_patch_20612_BE Guidance revision.doc, dated 8/21/2016 (Oct 2016 version). http://panorama.fda.gov/task/view?ID=5783f99e001740f37f79c4582354f2df  Lidocaine Patch Guidance_OCT2016.pc (*Recommended Dec 2006; Revised May 2007. Jul 2014; Jan 2016, Oct 2016*)	
Summary of OGD or DB History	Approved ANDAs:	Yes, 2 approved ANDAs A200675 (Actavis) A202346 (Mylan)
	Pending ANDAs:	Yes, 6 pending ANDAs (b) (4) A206463 (Amneal) A205882 (Kremers) A203265 (Noven) (b) (4) A209190 (Rhodes)* *current
	Controls:[5]	Yes
	Protocols:[6]	Yes

[5] OGD Control Database and Mercado, search: lidocaine patch, accessed on 05/20/2017.
[6] OGD-DB Protocols Tracking, search: lidocaine, accessed on 05/10/2017.
http://fdswv04385/seltrack/Protocols.asp

	Pending Citizen Petitions and other legal and regulatory issues:[7] If yes, please comment.	☐ Yes ☒ No

3.4 Pre-Study Bioanalytical Method Validation

Bioanalytical Method Validation for Plasma

Information Requested	Data
Bioanalytical method validation report location	Bioanalytical Repor (b) (4) - LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" For Fasted PK Study Protocol No. RP-LID-PK001; located in Module 5, Section 5.3.1.4. The filename is "rp-lid-pk-001-study-report" Validation for determination of lidocaine in plasma begins on page 1123 of 1260
Analyte	Lidocaine
Internal standard (IS)	Lidocaine-d_{10}
Method description	(b) (4)
Limit of quantitation (ng/mL)	
Average recovery of drug (%)	LQC: 98.3% MQC:100.0% HQC: 102.0% Avg: 100.1%
Average recovery of IS (%)	(b) (4) guidelines, if a stable isotope labeled IS was used, the recovery established for the un-labeled analyte will suffice and the recovery for the stable isotope labeled IS will not be required.[8]
Standard curve concentrations (ng/mL)	0.2 - 150 ng/mL
QC concentrations (ng/mL)	0.6 ng/mL, 45 ng/mL, and 112.5 ng/mL
QC Intra-run precision range (%CV)	Run 1: 1.0 to 7.7 Run 2: 0.7 to 3.6 Run 3: 1.4 to 7.0
QC Intra-run accuracy range (%Bias)	Run 1: 1.7 to 6.9 Run 2: -2.5 to 4.4

[7] Please check DLRS policy updates in the link http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx

(b) (4)

Information Requested	Data
	Run 3: -0.5 to 7.3
QC Inter-run precision range (%CV)	1.2 to 6.4
QC Inter-run accuracy range (%Bias)	-0.5 to 6.2
Bench-top stability (hours)	At least 15.5 hours at room temperature
Stock stability (hours/days)	6 hours at room temperature and under white light for lidocaine prepared in diluent (50:50 methanol/water) 28 days at 4 °C for lidocaine prepared in diluent (50:50 methanol/water)[9]
Processed stability (hours)	98.5 hours at room temperature
Freeze-thaw stability (freeze-thaw cycles)	3 freeze (-20 ºC)/thaw cycles
Long-term storage stability (days)	211 days at -20 °C[2]
Dilution integrity	1125 ng/mL diluted 10-fold
Selectivity	The selectivity evaluation met the acceptance criteria: no significant baseline interference (≥ 20% of the lower limit of quantitation, LLOQ for lidocaine or ≥ 5% of the IS peak area of the accepted calibration standards and QC samples for the IS) was detected at the retention times of lidocaine or the IS in blank human plasma. In addition, there was no interference from the analyte detected at the retention time of the internal standard.
Sample volume	50 µL
Regression	Least squares linear regression
Weighting	1/x*x concentration
Linearity	$R^2 \geq 0.9975$
Matrix Effect	IS-normalized matrix factor = 1.02 ± 0.05 at 0.6 ng/mL with %CV = 4.9% IS-normalized matrix factor = 0.97 ± 0.01 at 112.5 ng/mL with %CV = 1.0%
Hemolysis	The hemolysis evaluation met the acceptance criteria.
Reinjection reproducibility	102.5 hours at room temperature

Bioanalytical Method Validation for Cotton Swab

Information Requested	Data
Bioanalytical method validation report location	Bioanalytical Repor (b) (4) LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" For Fasted PK Study Protocol No. RP-LID-PK001; located in Module 5, Section 5.3.1.4. The filename is "rp-lid-pk-001-study-report" Validation for determination of lidocaine in cotton swab begins on page 1221 of 1260
Analyte	Lidocaine
Internal standard (IS)	Lidocaine-d_{10}

(b) (4)

Information Requested	Data
Method description	(b) (4)
Limit of quantitation (µg)	2.00 µg
Average recovery of drug (%)	105.0% at 6.00 µg 97.5% at 750 µg
Average recovery of IS (%)	(b) (4) guidelines, if a stable isotope labeled IS was used, the recovery established for the un-labeled analyte will suffice and the recovery for the stable isotope labeled IS will not be required.[8]
Standard curve concentrations (µg)	2.00 -1000 µg*
QC concentrations (µg)	6.00 µg, 300 µg, and 750 µg*
QC Intra-run precision range (%CV)**	Run 1: 1.0 to 3.4
	Run 2: 0.3 to 2.2
	Run 3: 0.8 to 3.0
QC Intra-run accuracy range (%Bias)**	Run 1: -1.3 to 7.5
	Run 2: -1.0 to 8.5
	Run 3: -3.3 to 4.0
QC Inter-run precision range (%CV)**	1.3 to 3.8
QC Inter-run accuracy range (%Bias)**	-1.8 to 5.5
Bench-top stability (hours)	NA
Stock stability (hours/days)	6 hours at room temperature and under white light for lidocaine prepared in diluent (50:50 methanol/water) 28 days at 4 °C for lidocaine prepared in diluent (50:50 methanol/water)[10]
Processed stability (hours)	NA
Freeze-thaw stability (freeze-thaw cycles)	NA
Long-term storage stability (days)	Lidocaine cotton swab samples would have the same stability as lidocaine itself. This would be expected to be at least as long as the established 211 days of plasma stability for lidocaine
Dilution integrity	NA
Selectivity	NA
Sample volume	50 µL
Regression	Least squares linear regression
Weighting	$1/x^2$
Linearity	$R^2 \geq 0.9989$
Reinjection reproducibility	65.5 hours at room temperature

*Based on 4 mL of extraction solution (1% formic acid in methanol) and followed by 500-fold dilution with diluent (50:50 methanol/water).

(b) (4)

**The intra-run and inter-run accuracy and precision ranges include the results from LLOQ, Low, Mid, and High QC samples.
Note: Due to the nature of the matrix (cotton swab) evaluated for this method the parameters marked as NA (not applicable) were not required for this validation.

Bioanalytical Method Validation for Patch

Information Requested	Data
Bioanalytical method validation report location	Bioanalytical Repor (b) (4) LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" For Fasted PK Study Protocol No. RP-LID-PK001; located in Module 5, Section 5.3.1.4. The filename is "rp-lid-pk-001-study-report" Validation for determination of lidocaine in patch begins on page 1182 of 1260
Analyte	Lidocaine
Internal standard (IS)	Lidocaine-d_{10}
Method description	(b) (4)
Limit of quantitation (mg)	1.00 mg (20 ng/mL lidocaine in diluent)
Average recovery of drug (%)	108%
Average recovery of IS (%)	(b) (4) guidelines, if a stable isotope labeled IS was used, the recovery established for the un-labeled analyte will suffice and the recovery for the stable isotope labeled IS will not be required.[8]
Standard curve concentrations (mg)	1.00 – 10.0 mg*
QC concentrations (mg)	3.00 mg, 6.00 mg, and 8.00 mg*
QC Intra-run precision range (%CV)**	Run 1: 0.8 to 1.5
	Run 2: 0.6 to 1.4
	Run 3: 0.8 to 1.6
QC Intra-run accuracy range (%Bias)**	Run 1: 1.2 to 4.7
	Run 2: -0.2 to 4.0
	Run 3: -0.7 to 2.0
QC Inter-run precision range (%CV)**	1.4 to 2.6
QC Inter-run accuracy range (%Bias)**	0.7 to 3.0
Bench-top stability (hours)	NA

Information Requested	Data
Stock stability (hours/days)	6 hours at room temperature and under white light for lidocaine prepared in diluent (50:50 methanol/water) 28 days at 4 °C for lidocaine prepared in diluent (50:50 methanol/water)[11]
Processed stability (hours)	NA
Freeze-thaw stability (freeze-thaw cycles)	NA
Long-term storage stability (days)	Lidocaine patch samples would have the same stability as lidocaine itself. This would be expected to be at least as long as the established 211 days of plasma stability for lidocaine
Dilution integrity	NA
Selectivity	NA
Sample volume	50 µL
Regression	Least squares linear regression
Weighting	No weighting
Linearity	$R^2 \geq 0.9988$
Reinjection reproducibility	89 hours at room temperature

*Based on 5 mL of extraction solution (1% formic acid in 50:50 dimethyl sulfoxide/methanol) and followed by 10000-fold dilution with diluent (50:50 methanol/water).
**The intra-run and inter-run accuracy and precision ranges include the results from LLOQ, Low, Mid, and High QC samples.
Note: Due to the nature of the matrix (patch) evaluated for this method the parameters marked as NA (not applicable) were not required for this validation.

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No (b) (4) General Guidelines for the Validation of Bioanalytical Methods, Effective date: 03/12/2012
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No K_2EDTA
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: Adequate

- The firm submitted the following acceptable addendum to the method validation repo (b) (4)

(b) (4)

[redacted] (b) (4)
Validation Report Addendum No.1 for Method [redacted] (b) (4) Stock Solution Storage Stability at 4°C and Long-term Sample Storage Stability Study at -20°C for Lidocaine in Human Plasma by LC/MS/MS.

- The firm did not provide the recovery for the Internal Standard (IS) Lidocaine-d_{10}. Per the firm' [redacted] (b) (4), General Guidelines for the Validation of Bioanalytical Methods, "*When a stable isotope labeled internal standard is used in an assay, the recovery established for the unlabeled analyte will suffice. Recovery for stable isotope labeled internal standards will not be required."* Lidocaine-d_{10} is an isotope labeled Lidocaine. Considering the recovery for the analyte lidocaine are very consisten [redacted] (b) (4) across different QC concentrations, the recovery of the IS (Lidocaine-d_{10}) is unlikely to impact the analytical results.

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL) Mean (SD)	T_{max} (hr) Median (Range)	$AUC_{0\text{-last}}$ (ng*hr/mL) Mean (SD)	$AUC_{0\text{-}\infty}$ (ng*hr/mL) Mean (SD)	T1/2 (hr) Mean (SD)	Kel (hr^{-1}) Mean (SD)	
Study RP-LID-PK-001	To assess the bioequivalence of a test formulation of lidocaine patch 5% versus Lidoderm®	Randomized, Open-Label, Single-Dose, Two-Period Crossover Study	Test product Strength: 3 x700 mg lidocaine patch 5% [Lot #L1304191]	48(25M/23 F) healthy subjects Age: mean (SD): 32.0(9.22); range: 18-45	71.68 (23.89)	12.00 (9 -21)	1268 (391.3)	1292 (392.2)	5.712 (1.193)	0.1271 (0.0298)	Clinical Study Report located in Module 5, Section 5.3.1.4. The filename is "rp-lid-pk001-report-body"
			Ref. product Lidoderm® Strength: 3 x 700 mg lidocaine patch 5% [Lot # Y2282]		76.19 (27.93)	12 (6 -21)	1330 (403.0)	1379 (385.6)	5.970 (1.370)	0.1221 (0.0282)	

Summary of Adhesion and Irritation Assessment of the Lidocaine Patch in the Fasting BE Study

According to the firm's BE study report No. RP-LID-PK001, patch adhesion was assessed 6 hours after application and within 30 min prior to patch removal using a visual scale (0-4). Evaluation of dermal reactions at the application sites was clinically assessed in a blinded fashion 30 minutes and 12 hours after patch removal using a visual irritation scale (0-7) that rated the degree of erythema, edema, and other signs of cutaneous irritation. The firm conducted statistical analysis of the cumulative adhesion index and differences in the cumulative adhesion index for Test vs. Reference formulations for safety population and the results are presented in the table below. The firm concluded that the test patch adheres better than the reference patch based upon the analysis.

	Mean (SD)		Least Square Means		Mean Test - Reference	90% Confidence Interval (T/R)
Patch Removal	**Test**	**Reference**	**Test**	**Reference**		
6 hours after application	0.333 (0.4673)	0.805 (0.9048)	0.333	0.805	-0.472	(-0.686, -0.258)
Within 30 minutes prior to patch removal	0.722 (0.8847)	1.514 (1.2922)	0.722	1.514	-0.792	(-1.066, -0.518)
Combined	0.528 (0.6563)	1.160 (1.0539)	0.528	1.160	-0.632	(-0.862, -0.402)

Data Source: Table 14.5.3 and Table 14.5.4

Table 14.3.3
Cumulative Skin Irritation Index by Treatment
Safety Population

		Treatment	
Parameter	Statistics	Lidocaine 5% topical patch 2100 mg (N = 48)	Lidoderm 2100 mg (N = 48)
Cumulative Skin Irritation Index	n	48	48
	Mean (SD)	0.19 (0.303)	0.19 (0.265)
	Median	0	0
	Min, Max	0, 1.0	0, 1.0

Note: The individual cumulative irritation index (CII) will be calculated as the sum of all dermal response scores for a treatment divided by the number of scores collected for that treatment.

There was assessment for local irritation 30 minutes and 12 hours after patch removal (individual data presented in Module 5.3.1.2. Listing Individual Laboratory Measurements by Patients). The reviewer verified from the irritation data that no incidence of severe irritation was observed and no patches were removed during the study due to any irritation reactions.

The firm conducted a separate study (No. RP-LID-SSI) to assess the skin irritation/sensitization/adhesion, and the data from the study will be reviewed by the DCR.

Summary of Residual Patch Analysis for Apparent Dose Delivered in the BE Study

Per the Product-Specific Guidance for Lidocaine Patch,[1] "*In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. Analyze and include in the calculation the amount of adhesive residue from each patch left on the skin.*"

In accordance with the Product-Specific Guidance for Lidocaine Patch, the apparent dose of lidocaine delivered was assessed by measurement of residual drug remaining on the used patches and from a swab of the area where the patches were applied. The individual and mean apparent dose of lidocaine in the study calculated by the firm is shown in the tables below.

Tables for Individual Residual Content and Apparent Dose (Submitted by the firm)

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	R	(b) (6)	8:00	0.624	1889	210.376
	2	T		8:00	1.51	1963	135.49
	1	R		8:02	0.542	1966	133.458
	2	T		8:02	0.724	1986	113.276
	1	T		8:04	0.388	2016	83.612
	2	R		8:04	0.892	1950	149.108
	1	T		8:06	0.0937	1961	138.9063
	2	R		8:06	0.666	1884	215.334
	1	R		8:08	2.35	1786	311.65
	2	T		8:08	2.5	1888	209.5
	1	T		8:10	0.96	1975	124.04*
	2	R		8:10	0.416	1973	126.584
	1	T		8:12	1.35	2010	88.65
	2	R		8:12	0.781	1865	234.219
	1	R		8:14	1.69	2041	57.31
	2	T		8:14	1.76	2032	66.24

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	T	(b) (6)	8:16	1.55	2035	63.45
	2	R		8:16	1.43	2007	91.57
	1	T		8:18	0.167	2049	50.833
	2	R		8:18	1.62	1825	273.38
	1	R		8:20	0.444	1899	200.556*
	2	T		8:20	1.42	1914	184.58
	1	R		8:22	0.141	2050	49.859
	2	T		8:22	0.218	2026	73.782
	1	T		8:24	1.49	1728	370.51
	2	R		8:24	3.85	1869	227.15
	1	T		8:26	0.409	1896	203.591
	2	R		8:26	1.46	1794	304.54
	1	R		8:28	0.853	1794	305.147
	2	T		8:28	0.727	1708	391.273
	1	R		8:30	0.923	1699	400.077
	2	T		8:30	0.28	1723	376.72

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	T	(b) (6)	8:32	0.847	1907	192.153
	2	R		8:32	1.98	1854	244.02
	1	R		8:34	2.38	1682	415.62
	2	T		8:34	0.677	1756	343.323
	1	T		8:36	0.919	1876	223.081
	2	R		8:36	1.57	1696	402.43
	1	R		8:38	0.736	1713	386.264
	2	T		8:38	0.325	1699	400.675
	1	R		8:40	0.829	1796	303.171
	2	T		8:40	0.907	1817	282.093
	1	R		8:42	0.194	1841	258.806
	2	T		8:42	0.886	1916	183.114
	1	T		8:44	1.97	1863	235.03
	2	R		8:44	2.02	1865	232.98
	1	T		8:46	0.593	1892	207.407
	2	R		8:46	1.77	1786	312.23

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	R	(b) (6)	8:48	2.21	1835	262.79
	2	T		8:48	1.57	1832	266.43
	1	T		8:50	0.0991	1903	196.9009
	2	R		8:50	0.163	1862	237.837
	1	R		8:52	1.62	1916	182.38
	2	T		8:52	1.42	1954	144.58
	1	T		8:54	0.561	1879	220.439
	2	R		8:54	0.45	1835	264.55
	1	R		8:56	3.52	1907	189.48
	2	T		8:56	2.01	1933	164.99
	1	R		8:58	0.866	1881	218.134
	2	T		8:58	2.08	1868	229.92
	1	T		9:00	0.537	1854	245.463
	2	R		9:00	0.287	1850	249.713*
	1	T		9:02	3.12	1952	144.88*
	2	R		9:02	0.417	1938	161.583*

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	T	(b) (6)	9:36	0.786	1906	193.214
	2	R		9:36	3.35	1857	239.65
	1	T		9:06	1.52	1947	151.48
	2	R		9:06	0.505	1936	163.495*
	1	R		9:08	2.27	1991	106.73*
	2	T		9:08	1.52	1968	130.48
	1	R		9:10	2.02	1852	245.98
	2	T		9:10	0.895	1900	199.105
	1	T		9:12	2.82	1800	297.18
	2	R		9:12	0.183	1851	248.817*
	1	R		9:14	1.54	1900	198.46*
	2	T		9:14	0.594	1866	233.406
	1	T		9:16	0.73	1871	228.27
	2	R		9:16	1.5	1851	247.5
	1	R		9:18	0.143	1909	190.857*
	2	T		9:18	1.31	1857	241.69

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	T	(b) (6)	9:20	1.73	1867	231.27
	2	R		9:20	1.54	1884	214.46
	1	T		9:22	0.351	1862	237.649
	2	R		9:22	0.616	1901	198.384
	1	R		9:24	1.23	1933	165.77
	2	T		9:24	0.4	1942	157.6
	1	R		9:26	1.4	1897	201.6
	2	T		9:26	0.29	1872	227.71
	1	T		9:28	3.64	1856	240.36
	2	R		9:28	3.79	1856	240.21
	1	R		9:30	2.55	1831	266.45
	2	T		9:30	0.707	1855	244.293
	1	T		9:38	0.924	2083	16.076
	2	R		9:38	0.72	1869	230.28
	1	R		9:34	1.45	1861	237.55
	2	T		9:34	0.487	1833	266.513

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Apparent Dose by Treatment – Safety Population (n=48) – Firm Submitted

		Treatment	
		Test	Reference
Apparent Dose (mg)	Mean (SD)	201.1 (88.85)	229.3 (80.18)

Apparent Dose– Safety Population (n=48) – Reviewer Calculated

The reviewer conducted calculation of the individual subjects' and mean apparent dose in Excel by subtracting the dose amount (3×700 mg=2100 mg) with residual drug remaining on the used patches and from a swab of the area where the patches were applied. The results are shown in the following table.

subject#	Test			Reference		
	Swab (mg)	Patch (mg)	Apparent Does (mg)	Swab (mg)	Patch (mg)	Apparent Does (mg)
(b) (6)	1.51	1963	135.49	0.624	1889	210.376
	0.724	1986	113.276	0.542	1966	133.458
	0.388	2016	83.612	0.892	1950	149.108
	0.0937	1961	138.9063	0.666	1884	215.334
	2.5	1888	209.5	2.35	1786	311.65
	0.96	1975	124.04	0.416	1973	126.584
	1.35	2010	88.65	0.781	1865	234.219
	1.76	2032	66.24	1.69	2041	57.31
	1.55	2035	63.45	1.43	2007	91.57
	0.167	2049	50.833	1.62	1825	273.38
	1.42	1914	184.58	0.444	1899	200.556
	0.218	2026	73.782	0.141	2050	49.859
	1.49	1728	370.51	3.85	1869	227.15

(b) (4)						
	0.409	1896	203.591	1.46	1794	304.54
	0.727	1708	391.273	0.853	1794	305.147
	0.28	1723	376.72	0.923	1699	400.077
	0.847	1907	192.153	1.98	1854	244.02
	0.677	1756	343.323	2.38	1682	415.62
	0.919	1876	223.081	1.57	1696	402.43
	0.325	1699	400.675	0.736	1713	386.264
	0.907	1817	282.093	0.829	1796	303.171
	0.886	1916	183.114	0.194	1841	258.806
	1.97	1863	235.03	2.02	1865	232.98
	0.593	1892	207.407	1.77	1786	312.23
	1.57	1832	266.43	2.21	1835	262.79
	0.0991	1903	196.9009	0.163	1862	237.837
	1.42	1954	144.58	1.62	1916	182.38
	0.561	1879	220.439	0.45	1835	264.55
	2.01	1933	164.99	3.52	1907	189.48
	2.08	1868	229.92	0.866	1881	218.134
	0.537	1854	245.463	0.287	1850	249.713
	3.12	1952	144.88	0.417	1938	161.583
	0.786	1906	193.214	3.35	1857	239.65
	1.52	1947	151.48	0.505	1936	163.495
	1.52	1968	130.48	2.27	1991	106.73
	0.895	1900	199.105	2.02	1852	245.98
	2.82	1800	297.18	0.183	1851	248.817
	0.594	1866	233.406	1.54	1900	198.46
	0.73	1871	228.27	1.5	1851	247.5
	1.31	1857	241.69	0.143	1909	190.857
	1.73	1867	231.27	1.54	1884	214.46
	0.351	1862	237.649	0.616	1901	198.384
	0.4	1942	157.6	1.23	1933	165.77
	0.29	1872	227.71	1.4	1897	201.6
	3.64	1856	240.36	3.79	1856	240.21
	0.707	1855	244.293	2.55	1831	266.45
	0.924	2083	16.076	0.72	1869	230.28
	0.487	1833	266.513	1.45	1861	237.55
Mean	**201.07**			**229.34**		
STD	**88.85**			**80.18**		
CV	**44.19**			**34.96**		
T-test	**0.052511997**					

The apparent dose values calculated by the reviewer are in agreement with the values submitted by the firm. The apparent dose of the test product is comparable to that of the reference product.

3.6 OSIS Status

The Office of Study Integrity and Surveillance (OSIS) recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (**NAI**). Therefore, the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within OSIS recommends accepting data without an on-site inspection.

Facility Type	Facility Name	Facility Address
Clinical	Frontage Laboratories	241 Main St., Hackensack, NJ
Analytical		(b) (4)

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	**RP-LID-PK001**
Study Title	A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine patch 5% and Lidoderm® in Healthy Adults under Fasted Conditions
Study Type	☒In Vivo BE ☐In Vitro BE ☐Permeability ☐Other
Submission Location: **Study Report**	Study report included in file "rp-lid-pk001-report-body" located in Module 5, Section 5.3.1.2.
Validation Report	See Bioanalytical Repor (b) (4) - LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" Validation Report begins on page 1123 as Report FRO-R2449R1 For Fasted PK Study Protocol No. RP-LID-PK001; located in Module 5, Section 5.3.1.4. The filename is "rp-lid-pk-001-study-report"
Bioanalytical Report	Bioanalytical Repor (b) (4) - LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" For Fasted PK Study Protocol No. RP-LID-PK001; located in Module 5, Section 5.3.1.4. The filename is "rp-lid-pk-001-study-report"
Clinical Site **(Name, Address, Phone #, Fax #)**	Frontage Clinical Services Frontage Laboratories, Inc 241 Main Street Hackensack, New Jersey 07601 USA Tel: 201-678-0288 Fax: 201-342-3413
Principal Clinical Investigator **(Name, Email)**	David Reiner, MD E-mail: dreiner@frontagelab.com
Dosing Dates	04-SEP-2013 11-SEP-2013
Analytical Site **(Name, Address, Phone #, Fax #)**	(b) (4)

	(b) (4)
Analysis Dates	Plasma analysis date: 19-SEP-2013, 20-SEP-2013, 23-SEP-2013, 24- SEP-2013, 25-SEP-2013, 26-SEP-2013* and 27-SEP-2013 Swab analysis date: 03-OCT-2013 and 05-OCT-2013 Patch analysis date: 04-OCT-2013, 07-OCT-2013, and 08-OCT-2013
Principal Analytical Investigator (Name, Email)	(b) (4)
Sample Storage : **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)**	Duration: Plasma: 23 days from the first sample collected on 04-SEP-2013 to the last sample analyzed on 27-SEP-2013 Cotton Swab: 31 days from the first sample collected on 04-SEP-2013 to the last sample analyzed on 05-OCT-2013. Patch: 34 days from the first sample collected on 04Sep13 to the last sample analyzed on 08-OCT-2013.
Sample Storage : **(b) Temperature Range (e.g., -20° C to -80° C)**	Temperature Range: -20 °C for plasma samples -20 °C for cotton swab samples Room temperature for patch samples
Long-Term Storage Stability Coverage (no. days @ temp °C)	211 days at -20 °C for lidocaine in human plasma
LTSS Data Location	Long-term Sample Stability is summarized in Module 5, Section 5.3.1.4 in the following report: Bioanalytical Report (b) (4) LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" The filename is "rp-lid-pk-001-study-report" Long term stability data are reported in the amendment included for this report which is title (b) (4) Validation Report Addendum No.1 for Metho (b) (4) which begins on page 1173 of 1260 of the Bioanalytical Report. LTSS Data are located on page 1178 of 1260 in Table 2.

* Incurred sample reproducibility (ISR) was performed on 26-SEP-2013

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	N/A	N/A
Product Name	Lidocaine Patch 5%	Lidoderm®
Manufacturer	Rhodes Pharmaceuticals L.P., manufactured by Altergon, Italia	Endo Pharmaceuticals, Inc. by (b) (4)
Batch/Lot No.	Lot number: L1304191	Lot number: Y2282
Manufacture Date	April 2013	N/A
Expiration Date	N/A	October 2015
Strength	5%	5%
Dosage Form	Topical patch	Topical patch
Bio-batch Size	(b) (4)	N/A
Production Batch Siz		N/A
Potency		(b) (4)
Content Uniformity (mean, %CV		N/A
Dose Administered	Dose was three patch simultaneously 3 × 700 mg	Dose was three patch simultaneously 3 × 700 mg
Route of Administration	Topical	Topical

Are the test and reference products expired at the time of study? **If Yes, please comment**	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? **If No, please comment**	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? **If No, please comment**	☒ Yes ☐ No
Is difference of the potency values for the Test and RLD within 5%? **If No, please comment**	☒ Yes ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 48 Dosed: 48 Completed: 48 Samples Analyzed: 48 Statistically Analyzed: 39*
No. of Sequences	2

No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Time 0 (within 90 minutes pre-application) and 1, 1.5, 2, 3, 6, 9, 12, 15, 18, 21, 24 and 48 hours after patch application. To determine the apparent dose delivered, a swab of patch adhesive was collected after patch removal. The swab and the used patches were analyzed for lidocaine concentrations.
IRB Approval	☒ Yes Date: 08/16/2013 ☐ No
Informed Consent	☒ Yes Date: 08/16/2013 ☐ No
Length of Fasting	Overnight fast of at least 10 hours
Length of Confinement	At least 10 hours before dosing up to 24 hours post-dose blood collection.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A All subjects received their assigned treatment as three topical patches applied simultaneously (2100 mg) to the infrascapular area of the back on either side of the spine, without occlusion, with approximately 2.5 cm between each patch for a total of 12 hours. Patches were applied by qualified study site personnel.
Safety Monitoring	☒ Yes ☐ No

***Reviewer's Note**: Per the firm's protocol No. RP-LID-PK001, the PK Population should consist of those subjects who completed both treatments without any major protocol violations, who provided plasma lidocaine concentration data sufficient to estimate PK parameters and had all 3 patches attached for ≥ 11 hours during each period. The reviewer confirmed that nine (9) subjects (Subject (b) (6)) had patch(es) that detached in less than 11 hours following application (module 5.3.1.2. Listing Individual Laboratory Measurements by Patient, Listing 16.2.8.3). These subjects were excluded from the PK population. Thirty-nine (81.3%) subjects were included in the statistical analysis.

Comments on Study Design: Adequate

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

		Study No. RP-LID-PK001	
		Treatment Groups	
		Test Product N = 48	Reference Product N = 48
Age (years)	Mean (SD)	32.0 (9.22)	32.0 (9.22)
	Range	18-45	18-45
Age Groups N (%)	< 18	0	0
	18 – 40	35 (72.9)	35 (72.9)
	40 – 64	13 (27.1)	13 (27.1)
	65 – 75	0	0
	> 75	0	0
Sex N (%)	Male	25 (52.1)	25 (52.1)
	Female	23 (47.9)	23 (47.9)
Race N (%)	White	29 (60.4)	29 (60.4)
	Black	19 (39.6)	19 (39.6)
BMI	Mean (SD)	25.32 (3.066)	25.32 (3.066)
	Range	18.1-29.9	18.1-29.9

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. RP-LID-PK001				
Subject No	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
NA	NA	NA	NA	NA

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasted Bioequivalence Study Study No. RP-LID-PK001	
	Test N=48 N (%)	**Reference N=48 N (%)**

Gastrointestinal disorders	**2 (4.2)**	**0**
Nausea	1 (2.1)	0
Vomiting	1 (2.1)	0
Nervous system disorders	**2 (4.2)**	**0**
Dizziness	1 (2.1)	0
Headache	1 (2.1)	0
Total	**2 (4.2)**	**0**

Subjects Experiencing Emesis

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
(b) (6)	T		(b) (6)		9.13

Were subjects who experienced vomiting included in statistical analysis?	☒ Yes ☐ No ☐ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☒ No ☐ N/A Since Lidocaine Patch is a topical product, the AE (vomiting) is not likely to have any impact on the overall study outcome.
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No The AEs experienced for the test product (nausea, dizziness, headache, vomiting) were listed in the Adverse Reaction section of the RLD label.[4]
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.1.2.4 Protocol Deviations

Study No. RP-LID-PK001		
Type	**Subject Number (Test)**	**Subject Number (Ref.)**
Period 1, Day 1, 3 hour post-application PK sample was collected 3 minutes out of the window	(b) (6)	
Period 2, Day 10, 48 hour post-application PK sample collection was not done		(b) (6)
Period 1, Day 3, 48 hour post-application PK sample was		

collected 36 minutes out of the window		
Period 2, Day 9, 18 hour post-application PK sample was collected 3 minutes out of the window	(b) (6)	

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Concomitant Medications:

Subject Number	First Dose Date	Any Con Med	ATC Class/ Reported Term	Indication	Dose	Unit	Freq[1]	ROA[2]	Start Date/ End Date	Continuing?
(b) (6)		Yes	Vitamin B-complex, incl. combinations/ Vitamin B	Dietary supplement	500	MCG	QD	Oral	(b) (6)	No
		Yes	Hormonal contraceptives for systemic use/ Mirena	Contraception	1	IUD	Every 5 years	Intrauterine		Yes
		Yes	Other nutrients/ Nutrament	Dietary supplement	355	ML	OTO	Oral		No

Comments on Clinical Results: Adequate

- Sampling time deviations were recorded during both periods of this study. These deviations were deemed to have no effect on the results of the study as all calculations were performed using the actual time points.
- Concomitant medications given during the study were confirmed to have no interaction with lidocaine per the RLD label.
- Protocol deviations and adverse events did not have impact on the study outcome.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Management and Use of Reference Standards for Bioanalytical Lab
		Tracking Procedure and Documentation for Biological Samples Received at Frontage Laboratories, Inc
		Handling Biological Samples Which May Contain Infectious Agents
		Evaluation of Incurred Sample Reproducibility (ISR)
		General Guidelines for the Validation of Bioanalytical Methods

(b) (4)	
	Criteria for Accepting Data From a Bioanalytical Run
	Repeat Assay and Reporting Criteria for Bioanalytical Samples
	Sample Analysis
	Rounding, Calculation and Reporting of Bioanalytical Data
	Use of the Sciex Analyst Mass Spectrometry Software
	Use of the Watson LIMS System at Frontage Laboratories, Inc.

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Summary of Standard Curve and QC Data for Plasma Sample

Bioequivalence Study No. RP-LID-PK001 Lidocaine							
Parameter	**Standard Curve Samples**						
Concentration (ng/mL)	0.200	0.400	1.00	5.00	30.0	60.0	120
Inter day Precision (%CV)	2.9	5.3	4.6	1.9	1.3	1.1	2.0
Inter day Accuracy (%Actual)	99.5	99.7	102.0	106.4	98.0	98.0	98.3
Linearity (Range of r^2 values)	0.9949 – 0.9992						
Linearity Range (ng/mL)	0.200 – 150						
Sensitivity/LOQ (ng/mL)	0.200						

Bioequivalence Study No. RP-LID-PK001 Lidocaine				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.600	45.0	113	1130
Inter day Precision (%CV)	8.9	3.3	3.5	NA*
Inter day Accuracy (%Actual)	97.5	98.2	94.7	90.3

*Not applicable, n=2 for Dilution QC samples

Summary of Standard Curve and QC Data for Cotton Swab Sample

Bioequivalence Protocol No. RP-LID-PK001 Lidocaine								
Parameter	**Standard Curve Samples**							
Concentration (µg)	2.00	4.00	8.00	40.0	200	400	800	1000
Inter day Precision (%CV)	4.4	9.5	3.1	2.0	2.0	0.7	1.2	1.1
Inter day Accuracy (%Actual)	96.5	103.8	105.4	105.5	103.5	100.3	94.9	90.5
Linearity (Range of r^2 values)	0.9949 – 0.9949							
Linearity Range (µg)	2.00 – 1000							
Sensitivity/ LOQ (µg)	2.00							

Bioequivalence Protocol No. RP-LID-PK001 Lidocaine			
Parameter	**Quality Control Samples**		
Concentration (µg)	6.00	300	750
Inter day Precision (%CV)	4.5	1.8	3.6
Inter day Accuracy (%Actual)	107.0	95.3	92.8

Summary of Standard Curve and QC Data for Patch Sample

Bioequivalence Protocol No. RP-LID-PK001 Lidocaine								
Parameter	**Standard Curve Samples**							
Concentration (mg)	1.00	2.00	4.00	6.00	7.00	8.00	9.00	10.0
Inter day Precision (%CV)	2.0	0.6	0.5	0.4	0.2	0.2	0.4	0.7
Inter day Accuracy (%Actual)	105.0	100.5	98.2	99.3	100.6	99.7	100.2	100.0
Linearity (Range of r^2 values)	0.9998 – 0.9998							
Linearity Range (mg)	1.00 – 10.0							
Sensitivity/ LOQ (mg)	1.00							

Bioequivalence Protocol No. RP-LID-PK001 Lidocaine			
Parameter	**Quality Control Samples**		
Concentration (mg)	3.00	6.00	8.00
Inter day Precision (%CV)	4.0	1.7	1.7
Inter day Accuracy (%Actual)	98.7	97.5	97.5

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No The firm provided chromatograms for the plasma sample for subject (b) (6) (12 out of 48) and all the chromatograms for the swab samples and the patch samples.
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No

Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Reanalysis of Plasma Samples

Study No. RP-LID-PK001
Additional Information in Module 5, Section 5.3.1.4
Bioanalytical Report No. (b) (4) - LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" Please see page 15 of 86.

Lidocaine

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	(b) (4)							
Reason A: the initial value was above the limit of quantitation*								
Reason B: the initial pre-dose value was not below LLOQ**								
Total								

Percentage was calculated based on Total Test or Reference Drug Study Sample.
*Pe (b) (4), Section 4.4.1
**Per (b) (4), Section 4.5.1

Reanalysis of Cotton Swap Samples

Protocol No. RP-LID-PK001
Additional Information in Module 5, Section 5.3.1.4
Bioanalytical Report No (b) (4) - LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" Please see 59 of 96.

Lidocaine

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetics	(b) (4)							
Reason A: The initial value was above the limit of quantitation*.								
Total for Sample Analysis								

*Per (b) (4), Section 4.4.1

Reanalysis of Patch Samples

Protocol No. RP-LID-PK001 Lidocaine								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetics	(b) (4)							
Total for Sample Analysis								

Note: Re-assay was not required for the patch samples.

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

For the plasma study samples, subjec (b) (6) (period 1 at 0 hrs) and subjec (b) (6) (period 2 at 0 hrs) were repeated for reason A: the initial value was above the limit of quantitation. Per SOP N (b) (4) "Repeat Assay and Reporting Criteria for Bioanalytical Samples", section 4.5.1, if the initial true pre-dose value or the control sample is not below LLOQ, the study sample should be repeated in duplicate. Both study samples were repeated in duplicate and the repeated values were below quantitation limit (BQL). For subjec (b) (6) (period 1 at 0 hrs), the initial concentration was (b) (4) approximately (b) (4) of the Cma (b) (4) If using the initial value, subjec (b) (6) should be excluded from the study because pre-dose concentration i (b) (4) of the Cmax. For subjec (b) (6) (period 2 at 0 hrs), the initial concentration wa (b) (4) of the Cma (b) (4). Subjec (b) (6) was excluded from the statistical analysis due to insufficient time of patch application (less than 11 hours). Therefore, those repeats are unlikely to impact the overall study outcome.

All the other samples reanalyzed for the BE study were analytical repeats following SOP N (b) (4), "Repeat Assay and Reporting Criteria for Bioanalytical Samples." No pharmacokinetic repeats were reported. The repeat analysis of the BE study is **adequate**.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters – Reviewer Calculated

Fasting Bioequivalence Study No. RP-LID-001									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
AUC0-t (hr *ng/ml)	(b) (4)								
AUC∞ (hr *ng/ml)									
Cmax (ng/ml									
Tmax* (hr)									
Kel (hr^{-1})									
T1/2 (hr)									

* Tmax values are presented as median, range

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Lidocaine Patch 5% Dose (3 x 700 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study No. RP-LID-001						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC0-t (hr *ng/ml	(b) (4)		(b) (4)			(b) (4)
AUC∞ (hr *ng/ml						
Cmax (ng/ml)						

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Lidocaine Patch 5% Dose (3 x 700 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study No. RP-LID-001						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	(b) (4)	3	(b) (4)	3		(b) (4)
AUC∞ (hr *ng/ml)		3		3		
Cmax (ng/ml)						

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	AUC (b) (4) AUCi (b) (4) Cmax (b) (4)
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)**	☐ Yes ☒ No
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed)**	☐ Yes ☒ No Please see comments on Bioanalytical Results
Are there first measurable drug concentration as Cmax? **If yes, please comment**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test		(b) (4)		
Reference				
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below	N/A			

Comments on PK results: Adequate

- The pharmacokinetic measures (AUCt, AUCi, Cmax, Tmax, KE and t1/2) and confidence intervals of AUCt, AUCi, and Cmax for **lidocaine** as calculated by the reviewer were in agreement with the values reported by the firm. The 90% confidence intervals for **lidocaine** of ln-transformed AUC_{0-t}, AUC_{∞} and C_{max} geometric mean test/reference ratios fall within the limits of 80-125%.

4.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Acceptable.

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study – Reviewer Calculated

Time (hr)	Test (n=39)		Reference (n=39)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.0	(b) (4)				
1.0					
1.5					
2.0					
3.0					
6.0					
9.0					
12.0					
15.0					
18.00					
21.00					
24.00					
48.00					

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

4.2 Formulation Data

4.2.1 Test Formulation

Ingredient	Function	% Formula	Milligrams Per Patch
Lidocaine	Active ingredient	5.00	700
Purified Wate	(b) (4)		(b) (4)
Glycerin			
Sorbito (b) (4)			
Polyacrylic Acid (b) (4)			
Sodium Polyacrylat			
Sodium Carboxymethylcellulos			
Propylene Glyco			
Urea			
Kaolin			
Tartaric Acid			
Gelatin			
Polyvinyl Alcohol (PVA			
Dihydroxyaluminium Aminoacetat			
Edetate Disodiu			
Methylparaben			
Propylparaben			
Total		**100.0**	

NDA 020612 Formulation[12] [NOT FOR RELEASE UNDER FOIA]

Ingredient	mg/g adhesive	mg/patch	Kg/batch	Purpose
Lidocaine	50	700	(b) (4)	active
(b) (4)				(b) (4)
Glycerin				
Sorbitol, (b) (4)				
Polyacrylic acid (b) (4)				
Sodium polyacrylate				
Sodium carboxymethyl cellulose				
Propylene glycol				
Urea				
Kaolin				
Tartaric acid				
Gelatin				
Polyvinyl alcohol				
Dihydroxyaluminum aminoacetate				
Disodium edetate				
Methylparaben				
Propylparaben				
Total				

4.2.2 Inactive Ingredients (IIG Table)

Components	mg/patch	Maximum amount (mg)/MDD (i.e. 3 patches/day)	IIG justification or limit (mg)
(b) (4)		(b) (4)	(b) (4) than RLD
Glycerin			Same as RLD
Sorbitol Solutio (b) (4)			Same as RLD
Polyacrylic Acid Solutio (b) (4)			Same as RLD
Sodium Polyacrylate			Same as RLD
Sodium Carboxymethyl Cellulose			(b) (4) than RLD Level acceptable per DCR

[12] Enterprise search: N020612, "N020612 REV 03-JUN-1996 1" Clinical Pharmacology/Biopharmaceutics Review. This is the current RLD formulation. The amount of each ingredient i (b) (4) batch size is same as the information in Chemistry Review of Supplement-10. DARRTS: NDA 20612, REV-QUALITY-03(General Review), 12/28/2006 (Supplement-10). Supplement 10 was approved on 2/19/07 (DARRTS: NDA 20612, COR-SNDAACTION-06(Approval CMC Supplement), 2/19/2007).

			Pharm/Tox Consult
Propylene Glycol	[redacted]	[redacted]	[redacted] as RLD
Urea			[redacted] as RLD
Kaolin			[redacted] as RLD
Tartaric Acid			[redacted] as RLD
Gelatin			[redacted] than RLD
Polyvinyl Alcohol (PVA)			[redacted] than RLD
Dihydroxyaluminium Aminoacetate			[redacted] than RLD**
Edetate Disodium			[redacted] as RLD
Methylparaben			[redacted] as RLD
Propylparaben			[redacted] as RLD

*A Pharm/Tox consult was sent to DCR from the Division of Filing Review (DFR) regarding if the proposed amount of Sodium Carboxymethyl Cellulose in the test formulation is acceptable.[13] Per the DCR Consultation [redacted] in the amount of Sodium Carboxymethyl Cellulose in the proposed formulation compared to the RLD is unlikely to affect the safety profile of the proposed formulation.[14]

**The maximum daily intake (MDI) of Dihydroxyaluminium Aminoacetate is justified based on ANDA 200675, Lidocaine Patch, 5% (Approval on 08/23/2012). The MDD of Lidocaine Patch is three patches/day, and the amount of Dihydroxyaluminium Aminoacetate is 35 mg/patch. Hence, the MDI of Dihydroxyaluminium Aminoacetate i [redacted]

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☐ Yes ☐ No ☒ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☐ Yes ☒ No
If no, are they all within IIG (per day) limits?	☐ Yes ☒ No ☐ N/A
If no, are additional data or Pharm/Tox consult necessary?	☒ Yes ☐ No ☐ N/A Consult outcome: level acceptable.
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☐ Yes ☐ No ☒ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

[13] ANDA-209190-ORIG-1, Filing Review, A209190N000DFR_Pharmtox.pdf, dated 6/3/2016
[14] GDRP, ANDA-209190-ORIG-1, Pharm/Tox Consult, A209190_DCRPT_ Lidocaine Patch 5% _CARBOXYMETHYLCELLULOSE-1.pdf, dated 5/10/2017. http://panorama.fda.gov/task/view?ID=570ff595000740d3dc5ece0916b35bb1&activeTab=list-task-documents
[15] DARRTS, ANDA 200675, REV-BIOEQ-01(General Review), dated 09/29/2011 and 04/26/2012.

Comments on Formulation: Acceptable

- The test product, Lidocaine Patch, 5% (b) (4)
- The formulation is **acceptable**.

4.3 Dissolution Testing

4.3.1 Dissolution Data

Dissolution Conditions	**Apparatus:**	5 (Paddle over disc)
	Speed of Rotation:	50 rpm
	Medium:	Acetic acid/Sodium acetate buffer, pH 4.0
	Volume:	500 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	[redacted] (b) (4) released after 0.5 hour	
Dissolution Testing Site (Name, Address)	Altergon Italia S.r.l. Zona Industriale, Morra de Sanctis Avellino 83040, Italy	

Study Ref No.	Testing Date	Product ID / Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	60	120	180	360	660	1440	Study Report Location
RT008-13	10/16/2013	Test Product: Lidocaine Patch 5% Lot# L1304191 Manufacture Date 04/2013	700 mg/patch	12	Mean	31	49	62	80	94	97	97	97	93	Module 2, Section 2.7, Report RT 008-13-02
					Rang	[redacted] (b) (4)									
					% CV	6.2	3.4	3.2	1.7	1.1	1.0	1.8	4.1	5.2	
RT008-13	10/24/2013	Reference Product: Lidoderm, Lot# Y2282 Expiry Date: 10/2015	700 mg/patch	12	Mean	32	46	60	77	92	97	97	96	90	
					Rang	[redacted] (b) (4)									
					% CV	12.1	7.2	5.8	5.1	3.5	4.7	2.1	1.5	2.2	

4.3.2 Dissolution Profiles

4.3.3 F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	The test product is a topical patch, and only has one (1) strength.

Overall Comments: Inadequate

- There is no USP dissolution method, but there is a FDA-recommended dissolution method for this drug product. The firm conducted dissolution testing using the FDA-recommended method [500 mL of Acetic Acid/Sodium Acetate Buffer, pH 4.0 at 32°C, with USP Apparatus V (Paddle over Disk) at 50 rpm].

- The firm's QC dissolution method and data were reviewed separately and found **inadequate.**[2]

4.4 Attachments

4.4.1 Additional Studies

Are there any additional studies? (e.g. pilot , failed) **If yes, please provide the location of report (complete/summary)**	☐ Yes ☒ No

4.4.2 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting	 209190_fasting_data.xlsx	 209190_fasting_CONTINU2.sas	 209190_Fasting_stat_LidocaineACTUAL.doc	 209190_Fasting_table_LidocaineACTUAL.doc

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 209190

APPLICANT: Rhodes Pharmaceuticals L.P.

DRUG PRODUCT: Lidocaine Patch, 5%

The Division of Bioequivalence (DB) II 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

4.5 Outcome

ANDA 209190

Reviewer: Wang, Yibo **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Lidocaine Patch, 5%

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
30811	4/14/2016	BIO	ANDA Original [1]	1	1
30811	4/14/2016	Parallel	Fasting Study (Full template) [1]	1	1
				Total:	2

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	209190
Product Name	Lidocaine Patch
Applicant	Rhodes Pharmaceuticals L.P.
Dosage Form/Strengths	Patch/5%
Route of Administration	Transdermal
Indication for Use	Relief of pain associated with post-herpetic neuralgia
Submission Date	September 26, 2017
Review Date	October 26, 2017
Primary Reviewer	Kelly M. Kitchens, Ph.D.
Secondary Reviewer	Tapash Ghosh, Ph.D.
Recommendation	**ADEQUATE**

1. REVIEW SUMMARY:

Background:
The firm is seeking approval of Lidocaine Patch, 5%, under the 505(j) path. Lidocaine Patch is indicated for relief of pain associated with post-herpetic neuralgia. The drug product is packaged as one patch in a child-resistant envelope with 30 envelopes per carton. The reference listed drug (RLD), Lidoderm® (lidocaine patch 5%), was approved under NDA 20612 for the 5% strength.

Submission:
This is a resubmission in response to the Complete Response (CR) letter dated July 7, 2017. The resubmission includes the firm's response to Biopharmaceutics deficiencies related to the drug release method validation, data, and acceptance criteria.

Review's Objective:
The Biopharmaceutics review is focused on the adequacy of the drug release method and acceptance criteria.

Reviewer's Assessment:
The drug release method and acceptance criteria are adequate.

Conclusion and Recommendation:
From the Biopharmaceutics perspective, ANDA 209190 for Lidocaine Patch, 5%, is recommended for approval.

2. REVIEW:

a) List Submissions being reviewed:

September 26, 2017	Resubmission, 1st minor complete response amendment

b) Highlight Key Outstanding Issues from Last Review Cycle: A Complete Response (CR) letter was issued on July 7, 2017 (see Appendix 2 for the Biopharmaceutics CR comments). In the CR letter, the Division of Biopharmaceutics requested additional information to support the drug release method validatio [redacted] (b) (4) and acknowledgement of their acceptance of the recommended drug release acceptance criteria.

c) Concise Description of Outstanding Issues: N/A

d) Drug Release method and acceptance criteria proposed by the Applicant:

Method Source	Diffusion Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times (minutes)	Acceptance criteria
FDA	USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10, 20, 30, 60, 120, 180, 360, 660, 1440	30 minutes [redacted] (b) (4) NLT [redacted] (b) (4) 1 hour [redacted] (b) (4): NLT [redacted] (b) (4) 2 hours [redacted] (b) (4) NLT [redacted] (b) (4)

e) Summary of Drug Release Data

Summary table of all the dissolution profiles

Batch	Mean % Lidocaine released at 10 minutes	Mean % Lidocaine released at 30 minutes	Mean % Lidocaine released at 60 minutes	Mean % Lidocaine released at 120 minutes	Mean % Lidocaine released at 180 minutes
L1304151	(b) (4)				
L1304191					
L1304201					
L1605301					
L16053111					
L16053112					
Min individual value from all batches					
Max individual value from all batches					
Average of all batches					

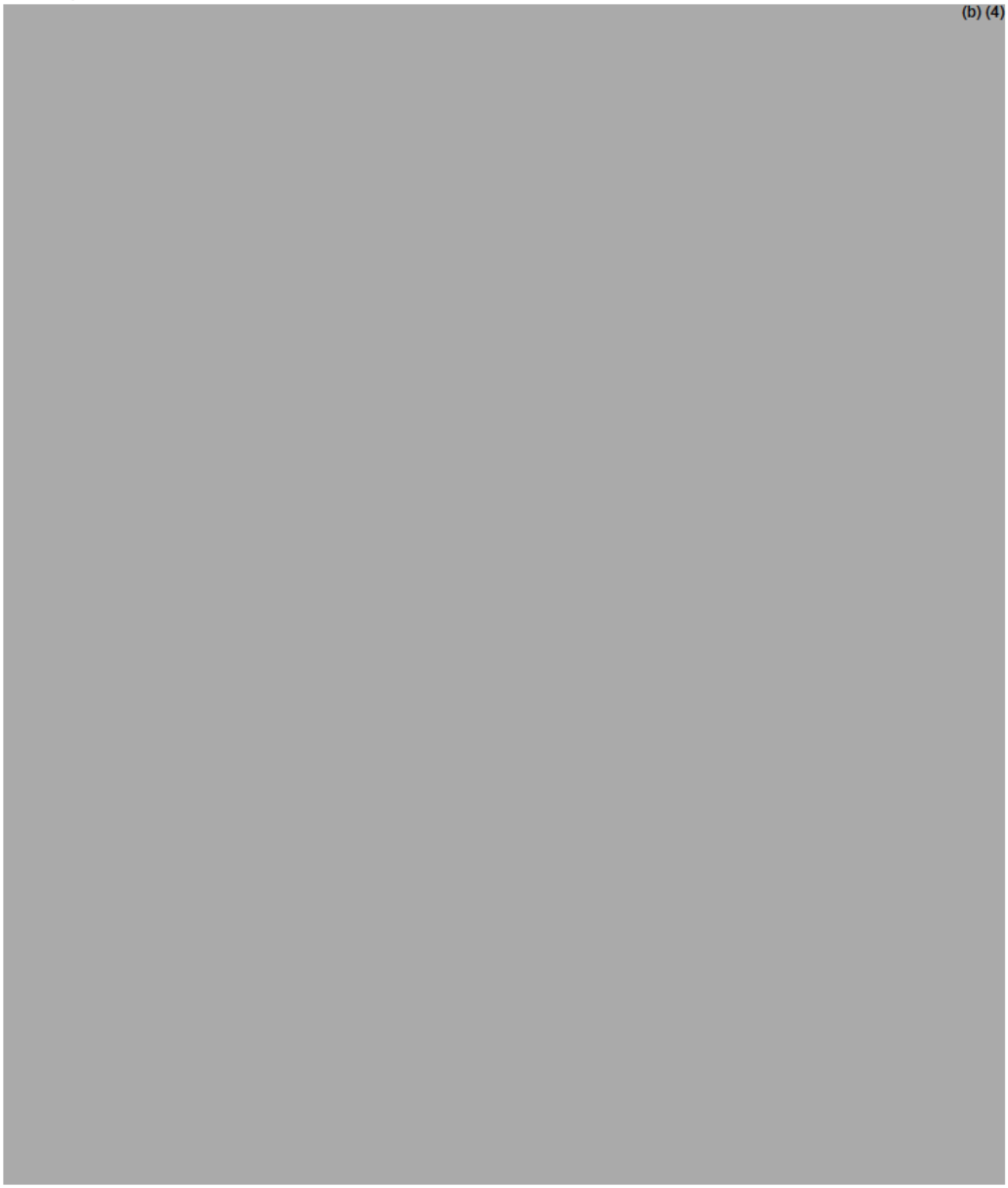
Refer to Appendix 1 for the tables of detailed drug release data.

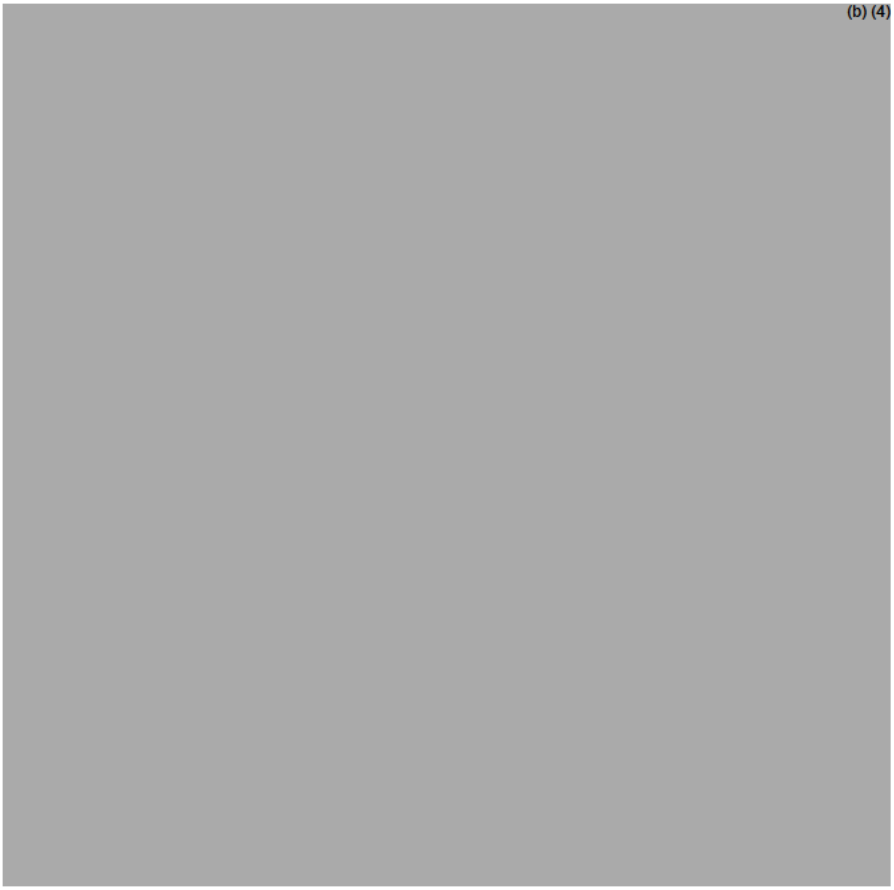
3. REVIEWER'S ASSESSMENT:

Reviewer's assessment of CR responses:

CR #1: The submitted chromatograms demonstrate that there are no interfering compounds with the analyte, Lidocaine.

(b) (4)





Thus, the drug release method is demonstrated to be specific.

CR #2: Linearity, as well as accuracy and repeatability precision, were validated in an appropriate rang (b) (4) for the drug release samples of lidocaine.

CR #3: The firm did not provide an adequate explanation as to why lidocaine release (b) (4) at the 24-hour time point. However, since drug release i (b) (4) at 24 hours, the drug release profile is adequate.

CR #4: The firm corrected the dilution factor of the standard from (b) (4)). The drug release method was revised accordingly and validated (Addendum Method Validation Report, Dissolution Test for Lidocaine Medicated Patches, Document # RMV-LAB-431-01-ADD01-Revision 01). Therefore, the firm provided additional drug release data (see Appendix 1) using the biobatch (L1304191), exhibit batches (L1304151 and L1304201), and validation batches (L1605301, L16053111, and L16053112) to support their proposed drug release acceptance criteria.

Time Point	Firm's original proposed	FDA-recommended	Firm's current proposed
10 minutes	---	NMT (b) (4)	**NMT** (b) (4)
30 minutes	NL (b) (4)	(b) (4)	(b) (4)
180 minutes	---	NLT (b) (4)	**NLT** (b) (4)

The firm's proposed acceptance criteria are adequate based on the drug release data (at release/T=0) submitted.

The firm's CR responses are **adequate**.

In Vitro Release Method: Adequate

In Vitro Release Acceptance Criteria: Adequate

4. LIST OF BIOPAHRMACEUTICS COMMENTS:

The firm developed and validated an adequate drug release method to measure the release of lidocaine from the drug product. Therefore, the drug release method is adequate. In addition, the firm's proposed drug release acceptance criteria are adequate based on the submitted drug release dat (b) (4) submitted. It is noted that the Drug Product reviewer has some deficiencies related to the drug release data during stability to be communicated to the firm.

5. CONCLUSION and RECOMMENDATION:

The following drug release method and acceptance criteria are recommended for the test product:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10 minutes: NMT (b) (4) 30 minutes (b) (4) 180 minutes: NLT (b) (4)

From the Biopharmaceutics perspective, ANDA 209190 for Lidocaine Patch, 5%, is recommended for approval.

6. SIGNATURE BLOCK:

Primary Biopharmaceutics Reviewer:
Kelly M. Kitchens, Ph.D., October 31, 2017

Secondary Biopharmaceutics Reviewer:
Tapash Ghosh, Ph.D., October 31, 2017

APPENDIX 1
In Vitro Release Data Tables

Batch L1304191

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L1304151

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L1304201

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L1605301

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L16053111

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L16053112

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

APPENDIX 2

Biopharmaceutics Information Requests and Firm Responses

Comments from July 7, 2017 CR letter:

Biopharmaceutics CR#1:
Submit the chromatograms generated for the specificity results of the drug release method validation (document number RMV LAB 431-03).

Firm's response to CR#1:
The following chromatograms are provided in section 3.2.P.5.3.

- Blank mobile phase chromatogram
- Placebo chromatogram
- Process standard solution chromatogram
- Reconstituted sample chromatogram

Biopharmaceutics CR#2:
Re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and report the linearity concentrations as percentage.

Firm's response to CR#2:
The analytical assay for linearity in a concentration range that covers the drug release sample concentrations has been revalidated. It was determined that the linearity, precision, and accuracy in the range o (b) (4) of the nominal active concentration was successfully carried out and validated. Refer to Addendum Method Validation Report, Dissolution Test for Lidocaine Medicated Patches, Document # RMV-LAB-431-01-ADD01- Revision 01, located in 3.2.P.5.3.

Biopharmaceutics CR#3:
Provide an explanation for th (b) (4) in drug release at the 1440-minute (24-hour) time point.

Firm's response to CR#3:
(b) (4) Given that the reference listed drug we believe that this is an artifact.

Biopharmaceutics CR#4:
Your proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:

10 minutes: NMT (b) (4)

30 minutes: Between (b) (4)
120 minutes: NLT (b) (4)

We request that you acknowledge your acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

Firm's response to CR#4:
Rhodes acknowledges the Agency's recommended drug release acceptance criteria; however, different acceptance criteria is being proposed based on the results from both the reference listed drug (LIDODERM®) and the test product as follows:

10 minutes: NMT (b) (4)
30 minutes: Between (b) (4)
180 minutes: NLT (b) (4)

Justification for these proposed specifications are explained in the Evaluation of Dissolution Data and Definition of Specifications, RA-LAB-2017-04 Rev. 01, located in 3.2.P.5.3.

Kelly Kitchens

Digitally signed by Kelly Kitchens
Date: 12/01/2017 07:28:01PM
GUID: 508da6fd0002849b46320c175775bdfa

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 12/04/2017 12:52:24PM
GUID: 508da7230002a2433ddcef616ca190df

Fred Echoles

Digitally signed by Fred Echoles
Date: 3/04/2020 02:05:47PM
GUID: 59d7e735007d9683178cc20188cfb7e4

BIOPHARMACEUTICS

Product Background: The firm is seeking approval of Lidocaine Patch, 5%, under the 505(j) path. Lidocaine Patch is indicated for relief of pain associated with post-herpetic neuralgia. The drug product is packaged as one patch in a child-resistant envelope with 30 envelopes per carton. The reference listed drug (RLD), Lidoderm® (lidocaine patch 5%), was approved under NDA 20612 for the 5% strength.

ANDA: 209190

Drug Product Name / Strength: Scopolamine Transdermal System Patch, 1.5 mg

Route of Administration: Transdermal

Applicant Name: Rhodes Pharmaceuticals L.P.

Review Summary:

The firm proposes to use the FDA-recommend drug release method for Lidocaine Patch. The drug release validation and proposed acceptance criteria are inadequate. Therefore, the following deficiencies will be conveyed to the firm:

1. Submit the chromatograms generated for the specificity results of the drug release method validation (document number RMV LAB 431-03).
2. Re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and report the linearity concentrations as percentage.
3. Provide an explanation for the (b) (4) in drug release at the 1440-minute (24-hour) time point.
4. Your proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:

10 minutes: NMT (b) (4)
30 minutes: Between (b) (4)
120 minutes: NLT (b) (4)

We request that you acknowledge your acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

List Submissions being reviewed (table):

Submission	Purpose of Submission
April 13, 2016	Original

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: See the list of deficiencies

BCS Designation

Reviewer's Assessment: The proposed product is a transdermal patch; therefore, BCS designation is not pertinent to this application.

Solubility:

Permeability:

Dissolution:

Drug Release Method and Acceptance Criteria

Reviewer's Assessment: INADEQUATE

- There is a FDA-recommended drug release method for this drug product:

Drug Release Conditions	Apparatus:	V (paddle over disk)
	Sinkers (If yes, type of sinkers)	No
	Speed of Rotation:	50 rpm
	Medium:	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C
	Volume:	500 mL

- The firm used the FDA-recommended drug release method to measure drug release of the test and RLD products.
- The analytical assay for the drug release testing was validated for system suitability, specificity, linearity and range, precision, accuracy, filtration study, solution stability, and robustness. Refer to Module 3.2.P.5.3. "Method Validation Report – Dissolution Test for Lidocaine Medicated Patches" for full details of the validation report.
    - There is an addendum to the validation report, since the drug release method was modified for the following after the original validation report was completed:
        - [redacted] (b) (4)
        - Sampling time change from 30 minutes to 30 minutes, 1 hour, and 2 hours; and,
        - Release specification for the new sampling times.
    - In the addendum, the analytical assay was validated for specificity, accuracy, and precision.

Drug Release Acceptance Criteria

- The firm proposed the following acceptance criterion: NLT (b) (4) released in 0.5 hour. Per the addendum method validation report, the firm will implement the following acceptance criteria (although this is not reported in the drug product specifications table):
  30 minutes (± 2%): NLT (b) (4)
  1 hour (± 2%): NLT (b) (4)
  2 hours (± 2%): NLT (b) (4)
- The firm provided complete drug release data (individual, mean, %CV, profile) for 12 units (non-pooled) of both the test and RLD products in the drug release testing.
  - Drug release testing was conducted on the biobatches of the test product (batch no. L1304191) and RLD (batch no. Y2282) products.
  - The test product batch was within 6 months old when testing was conducted, and the RLD product batch was unexpired at the time of drug release testing.

The drug release study results are summarized in the following table and drug release profile:

Dissolution Conditions	**Apparatus:**	5 (Paddle over disc)
	Speed of Rotation:	50 rpm
	Medium:	Acetic acid/Sodium acetate buffer, pH 4.0
	Volume:	500 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	(b) (4) released after 0.5 hour	
Dissolution Testing Site (Name, Address)	Altergon Italia S.r.l. Zona Industriale, Morra de Sanctis Avellino 83040, Italy	

Study Ref No.	Testing Date	Product ID / Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	60	120	180	360	660	1440	Study Report Location
RT008-13	10/16/2013	Test Product: Lidocaine Patch 5% Lot# L1304191 Manufacture Date 04/2013	700 mg/patch	12	Mean	31	49	62	80	94	97	97	97	93	Module 2, Section 2.7, Report RT 008-13-02
					Range	(b) (4)									
					% CV	6.2	3.4	3.2	1.7	1.1	1.0	1.8	4.1	5.2	
RT008-13	10/24/2013	Reference Product: Lidoderm, Lot# Y2282 Expiry Date: 10/2015	700 mg/patch	12	Mean	32	46	60	77	92	97	97	96	90	
					Range	(b) (4)									
					% CV	12.1	7.2	5.8	5.1	3.5	4.7	2.1	1.5	2.2	

(b) (4)

[redacted]

Reviewer's comments:

- The analytical method for drug release testing was adequately validated for system suitability, precision, accuracy, filtration study, solution stability, ands robustness.
  - The firm will be requested to submit the chromatograms generated for the specificity results of the drug release method validation (document number RMV LAB 431-03).
  - Linearity was validated in the concentration range (b) (4) The firm will be requested to re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and to report the linearity concentrations as percentage.
  - The sample solution is stable for up to 48 hours at room temperature.
  - The method is robust to small changes in flow rate, column temperature, mobile phase composition, and column from different suppliers.
- The firm will be requested to explain why drug releas (b) (4) at the 1440-minute (24-hour) time point.
- The firm's proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:
  10 minutes: NMT (b) (4)
  30 minutes: Betwee (b) (4)
  120 minutes: NLT (b) (4)
  The firm will be requested to acknowledge their acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

List of Deficiencies (IR#1):

1. Submit the chromatograms generated for the specificity results of the drug release method validation (document number RMV LAB 431-03).

2. Re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and report the linearity concentrations as percentage.
3. Provide an explanation for th (b) (4) in drug release at the 1440-minute (24-hour) time point.
4. Your proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:

   10 minutes: NMT (b) (4)
   30 minutes: Between (b) (4)
   120 minutes: NLT (b) (4)

   We request that you acknowledge your acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

Primary Biopharmaceutics Reviewer Name and Date:
Kelly M. Kitchens, Ph.D., February 13, 2017

Secondary Reviewer Name and Date:
Haritha Mandula, Ph.D., February 21, 2017

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 2/23/2017 01:17:06PM
GUID: 508da6fb000282df41459408f32a1ce0

Kelly Kitchens

Digitally signed by Kelly Kitchens
Date: 2/23/2017 01:31:04PM
GUID: 508da6fd0002849b46320c175775bdfa

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

STATISTICAL REVIEW

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

ADDENDUM TO STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number	ANDA 209190
Drug Name:	Lidocaine Patch 5%
Indication(s):	Relief of pain associated with post-herpetic neuralgia
Reference Listed Drug:	Lidoderm®
Applicant:	Rhodes Pharmaceuticals L.P.
Date(s):	Review Completion Goal Date: June 16, 2017
Biometrics Division:	Division of Biometrics VIII
Statistical Reviewer:	Somesh Chattopadhyay, Ph.D.
Secondary Reviewers:	Fairouz Makhlouf, Ph.D., Deputy Director
	Stella Grosser, Ph.D., Director
Medical Division:	Division of Clinical Review in the Office of Generic Drugs
Clinical Team:	Sunny Tse, Ph.D., Clinical Reviewer
	Carol Kim, Pharm.D., Clinical Team Leader
Addendum Reviewer:	Stella Grosser, Ph.D.
Reason for Addendum:	Following a meeting with the DCR review team, the statistical review team has revised its recommendation and now supports "adequate".

This memo serves to support a change in GDRP in the recommendation of the statistical reviewers for ANDA 209190. Following a June 8, 2017 meeting with the clinical review team in DCR/OB/OGD ("DCR"), the Division of Biometrics VIII in OB/OTS ("DBVIII") revises that recommendation and now considers the application adequate.

In our completed review of the ANDA, we identified deficiencies in the submitted irritation and sensitization study, Study RP-LID-SSI, and found the quality of the data to be so poor as to render any analyses meaningless. This led to an "inadequate" recommendation in GDRP.

On June 8, 2017, the review team in DBVIII held a meeting with the DCR ANDA clinical review team. In this meeting, the clinical team communicated that they determined other equivalence studies submitted to the ANDA, namely the PK and adhesion studies, were of sufficient quality, that the data in the ANDA support a conclusion of bioequivalence between the products, and that therefore the application could be approved. DBVIII reiterated that during review from a statistical standpoint, we determined the irritation and sensitization study RP-LID-SSI to have had numerous issues with the design, conduct and data quality. However, DBVIII communicated that we defer to and accept the DCR ANDA team's evaluation of the bioequivalence studies as a whole and that the totality of the evidence from a clinical point of view is favorable to the application.

Stella Grosser

Digitally signed by Stella Grosser
Date: 6/15/2017 01:29:37PM
GUID: 508da6d100025e36141b16fa39f28461

Fairouz Makhlouf

Digitally signed by Fairouz Makhlouf
Date: 6/15/2017 01:25:20PM
GUID: 508da6d000025d8d7f00c21ec50be7f0

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/Serial Number	ANDA 209190
Drug Name:	Lidocaine Patch 5%
Indication(s):	Relief of pain associated with post-herpetic neuralgia
Reference Listed Drug:	Lidoderm®
Applicant:	Rhodes Pharmaceuticals L.P.
Date(s):	Submitted: April 14, 2016
	Received by FDA: April 14, 2016
	Review Assignment: June 10, 2016
	Review Completion Goal Date: June 16, 2017
Biometrics Division:	Division of Biometrics VIII
Statistical Reviewer:	Somesh Chattopadhyay, Ph.D.
Secondary Reviewers:	Fairouz Makhlouf, Ph.D., Deputy Director
	Stella Grosser, Ph.D., Director
Medical Division:	Division of Clinical Review in the Office of Generic Drugs
Clinical Team:	Sunny Tse, Ph.D., Clinical Reviewer
	Carol Kim, Pharm.D., Clinical Team Leader

Keywords: active control/non-inferiority, endpoint analysis/LOCF, per protocol, missing data.

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant submitted results from two studies - an irritation and sensitization study (Study RP-LID-SSI) to evaluate the potential for skin irritation and sensitization of a test lidocaine 5% transdermal patch compared to the reference Lidoderm® 5% lidocaine patch in healthy adult subjects and a pharmacokinetic and adhesion study (Study RP-LID-PK001) to assess the bioequivalence of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus reference Lidoderm® topical patch after a 12-hour application in healthy adult male and female subjects under fasted conditions and to compare adhesive properties of the test and reference patches. The irritation and sensitization study RP-LID-SSI had numerous issues with the design, conduct and data quality. Due to design and conduct issues and inconsistencies within and between datasets, no single analysis population could be considered. The reviewer considered six different irritation analysis populations and six different sensitization analysis populations. The test patch showed non-inferiority to the reference patch with respect to mean irritation score in the induction phase in all of those irritation analysis populations (one-sided 95% upper confidence bound for Test -1.25*Reference using a linear model based on reviewer's analysis: -0.038 in two of the irritation analysis populations, -0.039 in three of the irritation analysis populations and -0.041 in one irritation analysis population). There was no sensitization reaction in any of the sensitization analyses. However, considering the extremely poor quality of data, the reviewer has no confidence in the correctness of the results. In the adhesion study RP-LID-PK001, the test patch showed non-inferiority to the reference patch with respect to mean adhesion score in the per protocol population (one-sided 95% upper confidence bound for Test - Reference using a linear mixed model based on reviewer's analysis: -0.4075).

1.2 Brief Overview of Clinical Studies

This review is based on two studies, RP-LID-SSI and RP-LID-PK001. Study RP-LID-SSI was a randomized, single-center, controlled, evaluator-blinded study to evaluate the potential for skin irritation and sensitization of a test lidocaine 5% transdermal patch compared to the reference Lidoderm® 5% lidocaine patch in healthy adult subjects. The study enrolled 248 healthy adult subjects at a single center (b) (4) in USA. The study had two phases: irritation/induction (Days 1-22) and sensitization/challenge (Days 36-41). Each subject was to receive both patches simultaneously on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the induction phase and on Day 36 during the challenge phase. Skin irritation was assessed using 'dermal response' and 'other effects' scores after each patch removal during the induction phase, and 30 minutes and 24, 48 and 72 hours after patch removal on Day 38. Primary evaluation of irritation was based on non-inferiority analysis of mean irritation score of the test patches against that of the reference patches during the induction phase. Evaluation of sensitization was based on the irritation scores during the challenge phase. The first subject was enrolled on (b) (6) (b) (6) and the last subject completed the study on (b) (6)

Study RP-LID-PK001 was a single-center, randomized, open-label, single-dose, two-period, crossover study to assess the bioequivalence of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus reference Lidoderm® topical patch after a 12-hour application in healthy adult male and female subjects under fasted conditions and to compare adhesive properties of the test and reference patches. The study enrolled 48 subjects at a single center (Hackensack, New Jersey) in USA. Each subject was randomized to one of two treatment sequences. In each study period, three test or three reference patches were applied simultaneously, for a 12-hour period, to the infrascapular area of the back on either side of the spine, without occlusion, with approximately 2.5 cm between each patch. Serial blood samples for determination of lidocaine plasma concentrations and PK analysis were obtained at time 0 (within 90 minutes pre-application) and 1, 1.5, 2, 3, 6, 9, 12, 15, 18, 21, 24 and 48 hours after patch application. Patch adhesion was assessed 6 hours (± 30 min) following patch application and within 30 minutes prior to patch removal using the FDA recommended 5-point adhesion rating scale. Primary evaluation of adhesion was based on non-inferiority analysis of mean adhesion score of the test patches against that of the reference patches. The study started on (b) (6) and the last subject completed the study o (b) (6).

1.3 Statistical Findings and Issues

In Study RP-LID-SSI, the test patch showed non-inferiority to the reference patch with respect to mean irritation score in the induction phase in six different irritation analysis populations (one-sided 95% upper confidence bound for Test -1.25*Reference using a linear model based on reviewer's analysis: -0.038 in two of the irritation analysis populations, -0.039 in three of the irritation analysis populations and -0.041 in one irritation analysis population). The non-inferiority analyses of irritation are presented in Table 26, Table 31, Table 36, Table 41, Table 46 and Table 51. No patch had a potential sensitization. In Study RP-LID-PK001, the test patch showed non-inferiority to the reference patch with respect to mean adhesion score (one-sided 95% upper confidence bound for Test - Reference using a linear mixed model based on reviewer's analysis: -0.4075). The non-inferiority analysis of adhesion is presented in Table 68.

Issues About Study RP-LID-SSI:

1. The quality of the submitted data in this application was extremely poor. There were numerous inconsistencies within and between datasets. The datasets contained incomplete information and many errors. Some of the errors were revealed by the applicant only after FDA asked for information or clarification about inconsistencies in the datasets in Easily Correctable Deficiency (ECD) letters. There are likely many more undetected errors in the datasets. Following are some examples.

a. The irritation and sensitizations analysis populations and reasons for exclusion from the analysis populations did not match between originally submitted datasets and the datasets submitted on December 9, 2016 in response to an ECD.
b. The adhesion score for a detached patch should be 4 based on the adhesion scale used in the study. The patch detachment flag and adhesion score were not consistent in the dataset q4-oct16.xpt submitted on December 9, 2016 (please see Table 11).
c. According to the original submission the test patch of Subjec (b) (6) and the reference patches of Subjects (b) (6) detached during the challenge phase. However, as shown in Table 10, based on the December 9, 2016 submission, the test patches of Subjects (b) (6) and the reference patch of Subjec (b) (6) detached during the challenge phase. These conflicting data give an indication of a possibility of reversing the test and reference data for some or all subjects in the dataset. If that happened, all analyses would be wrong. This gives a strong reason why inconsistent data should never be considered for an approval.
d. In the response to the statistical reviewer's request sent in an ECD letter, the applicant provided a list of patches that were detached and if a replacement patch was applied within 24 hours after detachment. The reviewer found out that for some subjects with detached patches in the list there was no information about detached patches in the data whereas the data contained the same information as the list for some other subjects. When the reviewer pointed it out in another ECD letter to the applicant, the applicant agreed that the dataset did not have the correct information and resubmitted the patch adhesion dataset.
e. The reviewer asked for clarification about a discrepancy that the patch removal date and time did not match between (b) (6) for some subjects. The applicant admitted the mistake and resubmitted the latter dataset.

2. Some data definition files did not have sufficient documentation and were not clear. Specifically, the variables AVAL and AVLC for each parameter in an ADaM dataset must be clearly defined. However, the data definition files did not have them. The applicant updated some data definition files in response to an FDA request for clarification of those variables for all parameters.

3. The information provided in some ECD responses was wrong or incomplete. Following are some examples.
    a. In response to an ECD letter, the applicant submitted a list subjects with detached patches. However, the reviewer found out that there were subjects with detached patches in the dataset that were not included in the list. When the reviewer pointed it out in a subsequent ECD letter to the applicant, the applicant replied that the subjects who had not completed the study were not included in that list. It appears that the applicant assumed that only the subjects that they thought would be included in the primary analysis had useful information. This is contrary to the good clinical practice.
    b. The reviewer noticed that the list of detached patches that the applicant provided in response to an ECD letter included a subject with detached patches that did not

have any detached patches according to the data. When the reviewer pointed it out in another ECD letter to the applicant, the applicant admitted that the subject was included in the list erroneously.

4. Subject (b) (6) withdrew from the study during the induction phase. In the dataset submitted on December 9, 2016, these subjects were correctly excluded from the per protocol population for irritation (PPPI) but included in the per protocol population for sensitization (PPPS) without any explanation.

5. Subjec (b) (6) completed the induction phase but was discontinued from the study by the investigator before the challenge phase. However, both patch types were included in the PPPS by the applicant in the dataset submitted on December 9, 2016.

6. The applicant did not submit the case report forms for Subjects (b) (6). Also the submitted case report forms contained many errors such as placing the irritation assessment date and score for one patch at a place designated for another patch. For example, the irritation assessment for the first set of patches was not done for Subject (b) (6) but the assessment date and scores were not left blank for that patch and the irritation assessment information for the second set of patches was placed at that place instead. Additionally, the case report forms had too many data clarification forms attached which not only shows the data collection and recording problems in the first place, it also makes the data prone to inaccuracy. This resulted in additional pages of protocol deviations where new protocol deviations are identified along with the already reported ones. The arrangement of these pages is not clearly explained by the applicant.

7. For Subject (b) (6), the irritation assessments on Day (b) (6) and Da (b) (6) were done 9 and 8 minutes, respectively, after patch removal. The case report form contains comments that these are out-of-window irritation assessments according to the protocol. According to the protocol (Section 4), skin irritation assessments were to occur within 15-30 minutes following removal of each patch during induction phase. Therefore, the comments about out-of-window irritation assessments during the induction phase in the CRF are not consistent with the protocol.

8. According to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion score of 3) during the induction phase, the skin irritation assessment for that patch was not to be included in the irritation analysis and the subject was to be scheduled for a make-up patch application. The protocol did not state if a make-up patch would be applied for the patches that completely detached (adhesion score of 4). However, make-up patches were applied for subjects who did not have any patch adhesion score of 3. It was noted as a protocol deviation by the applicant. However, the applicant did not adjust the analysis populations due to this deviation.

9. The Office of Study Integrity and Surveillance (OSIS) inspection report identified 12 subjects having an adhesion score of 4 (detached) and having a make-up patch. However,

Table 14 identifies many more subjects with make-up patches that were intended to replace the irritation scores of detached patches.

10. The OSIS inspection report states that except Subject [redacted] (b) (6), in other subjects who had a make-up patch for a detached patch, the inspection verified that the replacement patch had been detached for less than 24 hours. However, based on the data submitted on December 9, 2016, the reviewer could not confirm this. All patch detachment times were reported in the dataset as observed times as opposed to the actual times of detachment. In addition, the OSIS report is a direct contradiction to the ECD response submitted by the applicant on October 21, 2016. In response to Question 2 of the ECD letter, the applicant provided the following list of subjects who had detached patches for which date and time of detachment were unknown:

[redacted] (b) (6)

This list includes all 10 subject [redacted] (b) (6)) for which the OSIS report claimed that the patch was detached for less than 24 hours. Since for none of those subjects the time difference between the application time of the patch that detached and the application time of the next patch or a replacement patch is less than 24 hours, the OSIS report's verification claim is inaccurate unless the applicant submitted wrong information in that response and wrong datasets.

11. The OSIS inspection report identified only two subject [redacted] (b) (6) who would not have had nine irritation assessments if the make-up patches were not used. However, this review identified many more such subjects. Please refer to Table 9 for detached patches and Table 14 for make-up patches. It appears from the OSIS report that one of the reasons for excluding these subjects from the per protocol analysis is that these subjects have cumulative irritancy index (mean irritation score) greater than zero. The information about whether the cumulative irritancy index is greater than zero is irrelevant in this case. All subjects by this protocol deviation would be affected and affect the results in the same way no matter what the cumulative irritancy index is.

12. According to the protocol, if three patches of a subject were moved or removed for unacceptable degree of irritation during the induction phase, the subject was to be excluded from both the irritation and sensitization analyses of the product, and discontinued from study participation. However, FDA guidance recommends including those subjects in the irritation analysis using last observation carried forward (LOCF). No subject was discontinued due to excessive irritation in this study.

13. According to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion score of 3) during the induction phase, the skin irritation assessment for that patch was not to be included in the irritation analysis and the subject was to be scheduled

for a make-up patch application. It is understood that the irritation score from a make-up patch would replace the irritation score of the patch that was <50% adhered but not detached if only a single patch out of 9 patches had <50% adherence without being detached. However, the protocol did not state how the irritation scores would be used when two or more patches of the same type for the same person had <50% adherence without being detached. In response to an ECD (ECD letter date: September 16, 2016, ECD response date: September 29, 2016), the applicant stated that when there were multiple patches of the same type with an adhesion score of 3 for the same subject, a single make-up patch was applied and the irritation score for the make-up patch replaced the irritation scores of all the patches with an adhesion score of 3 that the make-up patch replaced. The applicant adjusted the number of irritation assessments by counting the number of patches not having an adhesion score of 3 and adding one for the make-up patch to that count. For example, if there are 3 patches with an adhesion score of 3, then the number of irritation scores used to calculate the mean would be 6+1=7. In the reviewer's opinion, this is not an appropriate method to calculate the mean irritation score since it essentially reduces the number of irritation scores unless there is only one patch with an adhesion score of 3. The particular patch type for that subject should be excluded from the irritation and sensitization analyses.

14. The study design did not follow the Draft Guidance on Lidocaine. According to the guidance, patches should be applied on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the induction phase. The patches should be assessed for irritation after patch removal and before new patch application. Patches applied on Day 19 should be assessed on Day 22. Based on the protocol, the subjects were allowed to skip a visit and keep the patches on until the next visit when they were evaluated for skin irritation. It resulted in having the same patch on for 4 or 5 days before an irritation assessment while the patches without a skipped visit were on for 2 or 3 days before the irritation assessment.

15. According to the protocol, the subjects who did not return for one visit to the study site during the induction phase were instructed to keep the patches in place. They were scheduled to receive a make-up patch application at the last visit during the induction phase. The study report did not clearly differentiate the dual use of the terminology "make-up patch" for two different purposes. In the first case, the irritation score of the make-up patch is intended to replace the irritation score of a partially detached (<50% adhesion but not completely detached) patch. In the second case, the make-up patch is simply intended to be an additional patch when a visit was skipped to make a total of 9 patches during the induction phase.

16. According to the protocol, a subject who missed the ninth assessment but had 9 patch applications was considered to have completed the induction phase, and the last observed irritation score (the irritation score for the eighth patch) was carried forward. This approach contradicts the Draft Guidance on Lidocaine since the guidance requires application and evaluation of all 9 patches unless the patch removal is due to excessive irritation. In the reviewer's opinion the subjects who missed the ninth assessment should be excluded from the irritation and sensitization analyses.

17. The protocol specified that hypoallergenic tape would be applied to all four edges of each patch. However, there was no mention of this reinforcement tape in the clinical study report. In response to an ECD (ECD letter date: August 23, 2016, ECD response date: September 6, 2016), the applicant confirmed that the hypoallergenic tape was used on all four edges and diagonally on all patches.

18. The applicant used a different rating scale for "other effects" than what is recommend by FDA in Draft Guidance on Lidocaine. Although the other effects categories are identical between the applicant's and FDA's scales, the numerical values associated with the categories based on the applicant's scale are higher with a wider range than those based on the FDA's scale. The applicant did not use any letter score for the other effects. The other effects rating scales based on the applicant and FDA are presented side by side in Table 4. The applicant's other effects rating scale increases the irritation score (dermal response score + other effects score). This increased irritation score makes both the numerator and denominator of the test statistic, which is a ratio (Test/Reference), larger and thus the ratio closer to one numerically. Therefore, the test is more likely to be found non-inferior to the reference with the applicant's rating scale. The reviewer used the FDA-recommended scale for the analyses of irritation and sensitization.

19. According to the Draft Guidance on Lidocaine, the applicant should provide a frequency table showing the number of applications of each test article with each combined dermal response and other effects score using the last observation carried forward (LOCF) for subjects who discontinued a test article because of unacceptable irritation. The applicant did not provide any such table.

20. The Draft Guidance on Lidocaine states the following: "To demonstrate non-inferiority of the test product compared to the RLD with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score must be less than or equal to 0." However, the applicant's criterion for non-inferiority in the primary analysis was different. The applicant considered the test product to be non-inferior to the reference product if the upper bound of the one-sided 95% confidence interval of the difference between the products (test - reference) was not greater than 0.11. The applicant did not provide any justification in the protocol, statistical analysis plan or clinical study report for its criterion for non-inferiority in the primary analysis and how they determined the non-inferiority margin of 0.11.

Issues About Study RP-LID-PK001:

1. It should be noted that the rightmost column of Table 11-4 in the clinical study report has a column heading "90% Confidence Interval (T/R)". After checking the source Table 14.5.4 in the clinical study report and the SAS code that generated that table, the reviewer concluded that the rightmost column heading in Table 11-4 is incorrect. It should be "90% Confidence Interval (T - R)". Table 64 shows the correct column heading.

2. There was one patch where the adhesion score decreased from the 6 hour assessment to 12 hour assessment. The applicant did not adjust the adhesion score for that patch in the analysis.

1.4 Comments About the Application

We have identified the following issues with Study RP-LID-SSI.

1. The quality of the submitted data in this application was extremely poor. There were numerous inconsistencies within and between datasets. The datasets contained incomplete information and many errors. Some of the errors were discovered only after FDA asked for information or clarification about inconsistencies in the datasets in Easily Correctable Deficiency (ECD) letters. There are likely many more undetected errors in the datasets. FDA does not have any confidence in the correctness of the datasets and any analyses based on the submitted data. Following are some examples of inconsistencies and errors.
    a. The irritation and sensitizations analysis populations and reasons for exclusion from the analysis populations did not match between originally submitted datasets and the datasets submitted on December 9, 2016.
    b. The adhesion score for a detached patch should be 4 based on the adhesion scale used in the study. The patch detachment flag and adhesion score were not consistent in the dataset q4-oct16.xpt submitted on December 9, 2016.
    c. According to the original submission the test patch of Subjec (b) (6) and the reference patches of Subjects (b) (6) detached during the challenge phase. However, based on the December 9, 2016 submission, the test patches of Subjects (b) (6) and the reference patch of Subjec (b) (6) detached during the challenge phase. These conflicting data give an indication of a possibility of reversing the test and reference data for some or all subjects in the dataset. If that happened, all analyses would be wrong.
    d. In the response to an ECD letter, the applicant provided a list of patches that were detached and if a replacement patch was applied within 24 hours after detachment. We found out that for some subjects with detached patches in the list there was no information about detached patches in the data whereas the data contained the same information as the list for some other subjects. When we pointed it out in another ECD letter, the applicant acknowledged that the dataset did not have the correct information and resubmitted the patch adhesion dataset.
    e. We asked for clarification about a discrepancy that the patch removal date and time did not match between ex.xpt and adph.xpt for some subjects. The applicant acknowledged the mistake in the dataset.
    f. Subjects (b) (6) withdrew from the study during the induction phase. In the dataset submitted on December 9, 2016, these subjects

were correctly excluded from the per protocol population for irritation (PPPI) but included in the per protocol population for sensitization (PPPS) without any explanation.

g. Subjec (b) (6) completed the induction phase but was discontinued from the study by the investigator before the challenge phase. However, both patch types were included in the PPPS by the applicant in the dataset submitted on December 9, 2016.

2. There were many issues with the design and analysis of this study. Some of them cannot be corrected after completion of the study. We recommend that the applicant conduct a new irritation and sensitization study following the Draft Guidance on Lidocaine. Following are some design and analysis issues we have identified.

   a. The study design did not follow the Draft Guidance on Lidocaine. According to the guidance, patches should be applied on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the induction phase. The patches should be assessed for irritation after patch removal and before new patch application. Patches applied on Day 19 should be assessed on Day 22. Based on the protocol, the subjects were allowed to skip a visit and keep the patches on until the next visit when they were evaluated for skin irritation. It resulted in having the same patch on for 4 or 5 days before an irritation assessment while the patches without a skipped visit were on for 2 or 3 days before the irritation assessment. The applicant should not allow any skipped visit in any future irritation/sensitization studies.

   b. According to the protocol, a subject who missed the ninth assessment but had 9 patch applications was considered to have completed the induction phase, and the last observed irritation score (the irritation score for the eighth patch) was carried forward. This approach contradicts the Draft Guidance on Lidocaine since the guidance requires application and evaluation of all 9 patches unless the patch removal is due to excessive irritation. The subjects who missed the ninth assessment should be excluded from the irritation and sensitization analyses.

   c. According to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion score of 3) during the induction phase, the skin irritation assessment for that patch was not to be included in the irritation analysis and the subject was to be scheduled for a make-up patch application. It is understood that the irritation score from a make-up patch would replace the irritation score of the patch that was <50% adhered but not detached if only a single patch out of 9 patches had <50% adherence without being detached. However, the protocol did not state how the irritation scores would be used when two or more patches of the same type for the same person had <50% adherence without being detached. The applicant stated in the ECD response dated September 29, 2016 that when there were multiple patches of the same type with an adhesion score of 3 for the same subject, a single make-up patch was applied and the irritation score for the make-up patch replaced the irritation scores of all the patches with an adhesion score of 3 that the make-up patch replaced. This is not an appropriate method to calculate the mean irritation score since it essentially reduces the number of irritation scores unless there is only one patch with an adhesion score of 3. We recommend the

applicant to not use any make-up patch in any future irritation/sensitization studies.

d. The applicant used a different rating scale for "other effects" than what is recommend by FDA in Draft Guidance on Lidocaine. Although the other effects categories are identical between the applicant's and FDA's scales, the numerical values associated with the categories based on the applicant's scale are higher with a wider range than those based on the FDA's scale. Also the applicant did not use any letter score for the other effects. The other effects letter score and numeric scale should be used as recommended in the Draft Guidance on Lidocaine.

e. According to the protocol, if three patches of a subject were moved or removed for unacceptable degree of irritation during the induction phase, the subject was to be excluded from both the irritation and sensitization analyses of the product, and discontinued from study participation. However, FDA's Draft Guidance on Lidocaine recommends including those subjects in the irritation analysis using last observation carried forward (LOCF). Although no subject was discontinued due to excessive irritation in this study, it should be corrected in any future irritation/sensitization studies.

f. The Draft Guidance on Lidocaine states the following: "To demonstrate non-inferiority of the test product compared to the RLD with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score must be less than or equal to 0." However, the applicant's criterion for non-inferiority in the primary analysis was different. The applicant considered the test product to be non-inferior to the reference product if the upper bound of the one-sided 95% confidence interval of the difference between the products (test - reference) was not greater than 0.11. The applicant did not provide any justification in the protocol, statistical analysis plan or clinical study report for this criterion and how the non-inferiority margin of 0.11 is determined.

3. There were some issues with the study conduct. Following are some examples.

a. According to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion score of 3) during the induction phase, the skin irritation assessment for that patch was not to be included in the irritation analysis and the subject was to be scheduled for a make-up patch application. The protocol did not state if a make-up patch would be applied for the patches that completely detached (adhesion score of 4). However, make-up patches were applied for subjects who did not have any patch adhesion score of 3. The applicant noted it as a protocol deviation. However, the applicant did not adjust the analysis populations due to this deviation.

b. For Subjec (b) (6), the irritation assessments on Da (b) (6) and Da (b) (6) were done 9 and 8 minutes, respectively, after patch removal. The case report form contains comments that these are out-of-window irritation assessments according to the protocol. According to the protocol (Section 4), skin irritation assessments were

to occur within 15-30 minutes following removal of each patch during induction phase. Therefore, the comments about out-of-window irritation assessments during the induction phase in the CRF are not consistent with the protocol.

4. The quality of the submission was poor. The study report did not provide some necessary information. The data definition files did not contain complete information. Also the applicant's responses to the ECDs were sometimes incomplete and contained errors. Following are some examples.
    a. Some data definition files did not have sufficient documentation and were not clear. Specifically, the variables AVAL and AVLC for each parameter in an ADaM dataset must be clearly defined. However, the data definition files did not have them. The applicant updated some data definition files in response to an FDA request for clarification of those variables for all parameters.
    b. The applicant did not submit the case report forms for Subjects (b) (6). Also the submitted case report forms contained many errors such as placing the irritation assessment date and score for one patch at a place designated for another patch. For example, the irritation assessment for the first set of patches was not done for Subjec (b) (6) but the assessment date and scores were not left blank for that patch and the irritation assessment information for the second set of patches was placed in that place instead. Additionally, the case report forms had too many data clarification forms attached which not only shows the data collection and recording problems in the first place, it also makes the data prone to inaccuracy. This resulted in additional pages of protocol deviations where new protocol deviations are identified along with the already reported ones. The arrangement of these pages is not clearly explained.
    c. According to the protocol, the subjects who did not return for one visit to the study site during the induction phase were instructed to keep the patches in place. They were scheduled to receive a make-up patch application at the last visit during the induction phase. The study report did not clearly differentiate the dual use of the terminology "make-up patch" for two different purposes. In one case, the irritation score of the make-up patch is intended to replace the irritation score of a partially detached (<50% adhesion but not completely detached) patch. In the other case, the make-up patch is simply intended to be an additional patch when a visit was skipped to make a total of 9 patches during the induction phase.
    d. The protocol specified that hypoallergenic tape would be applied to all four edges of each patch. However, there was no mention of this reinforcement tape in the clinical study report. In the ECD response dated September 6, 2016, the applicant confirmed that the hypoallergenic tape was used on all four edges and diagonally on all patches. This information should have been included in the clinical study report.
    e. In the study report and analysis results, the applicant should provide a frequency table showing the number of applications of each test article with each combined dermal response and other effects score using the last observation carried forward (LOCF) for subjects who discontinued a test article because of unacceptable

irritation (refer to the Draft Guidance on Lidocaine which recommends providing this table).

f. In response to an ECD letter, the applicant submitted a list subjects with detached patches. However, we found out that there were subjects with detached patches in the dataset that were not included in the list. When we pointed it out in a subsequent ECD letter to the applicant, the applicant replied that the subjects who had not completed the study were not included in that list. It appears that the applicant assumed that only the subjects that the applicant thought would be included in the primary analysis had useful information. All data and information should be submitted even if the applicant does not think it may be useful.

g. We noticed that the list of detached patches that the applicant provided in response to an ECD letter included a subject with detached patches that did not have any detached patches according to the data. When we pointed it out in another ECD letter, the applicant acknowledged that the subject was included in the list erroneously.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

Lidoderm® (lidocaine patch 5%) is indicated for relief of pain associated with post-herpetic neuralgia. The patch is comprised of an adhesive material containing 5% lidocaine (700 mg) in an aqueous base. It is applied as up to three patches for up to 12 hours within a 24-hour period, directly to intact skin, to cover the most painful areas. Lidocaine, chemically designated as acetamide, 2-(diethylamino)-N-(2, 6-dimethylphenyl), is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. The amount of lidocaine absorbed from Lidoderm® is directly related to the duration of application and the surface area over which the patch (es) are applied. When used as directed, only 3 ± 2% of the dose applied is expected to be absorbed, meaning at least 95% (665 mg) of the lidocaine will remain in each used patch. The recommended maximum daily dose of three patches applied simultaneously over a 12-hour period results in a mean peak blood concentration of lidocaine of approximately 0.13 μg/mL, and patch application for three consecutive days does not result in increased lidocaine concentration.

In this ANDA application, Rhodes Pharmaceuticals L.P. is seeking approval of a generic version of the lidocaine 5% topical patch.

2.1.2 Regulatory History

The reference listed drug Lidoderm® was approved under NDA-020612 on March 19, 1999. (b) (4) Subsequently, the applicant submitted ANDA 209190 on April 14, 2016 for the same product including the same irritation and sensitization study (RP-LID-SSI) and the same pharmacokinetic and adhesion study (RP-LID-PK001). (b) (4)

2.1.3 Specific Studies Reviewed

The applicant submitted results from two studies - an irritation and sensitization study (Study RP-LID-SSI) and a pharmacokinetic and adhesion study (Study RP-LID-PK001). This review is based on both studies.

Study RP-LID-SSI was a randomized, single-center, controlled, evaluator-blinded study to evaluate the potential for skin irritation and sensitization of a test lidocaine 5% transdermal patch compared to the reference Lidoderm® 5% lidocaine patch in healthy adult subjects. The study enrolled 248 healthy adult subjects. The study had two phases: irritation/induction (Days 1-22)

and sensitization/challenge (Days 36-41). Each subject was to receive both patches simultaneously on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the induction phase and on Day 36 during the challenge phase. Skin irritation was assessed using 'dermal response' and 'other effects' scores after each patch removal during the induction phase, and 30 minutes and 24, 48 and 72 hours after patch removal on Day 38. Subjects were enrolled at a single center (b) (4) in USA.

Study RP-LID-PK001 was a single-center, randomized, open-label, single-dose, two-period, crossover study to assess the bioequivalence of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus reference Lidoderm® topical patch after a 12-hour application in healthy adult male and female subjects under fasted conditions and to compare adhesive properties of the test and reference patches. The study enrolled 48 subjects. Each subject was randomized to one of two treatment sequences. In each study period, three test or three reference patches were applied simultaneously, for a 12-hour period, to the infrascapular area of the back on either side of the spine, without occlusion, with approximately 2.5 cm between each patch. Serial blood samples for determination of lidocaine plasma concentrations and PK analysis were obtained at time 0 (within 90 minutes pre-application) and 1, 1.5, 2, 3, 6, 9, 12, 15, 18, 21, 24 and 48 hours after patch application. Patch adhesion was assessed 6 hours (± 30 min) following patch application and within 30 minutes prior to patch removal using the FDA recommended 5-point adhesion rating scale. Subjects were enrolled at a single cente (b) (4) in USA.

2.2 Data Sources

Data used for this review are from the electronic submissions dated April 14, 2016, May 23, 2016, October 21, 2016 and December 9, 2016. The paths are as follows:
\\Cdsesub1\Evsprod\ANDA209190\0000\m5\datasets\rp-lid-ssi,
\\Cdsesub1\Evsprod\ANDA209190\0000\m5\datasets\rp-lid-pk001,
\\Cdsesub1\Evsprod\ANDA209190\0001\m5\datasets\rp-lid-ssi,
\\Cdsesub1\Evsprod\ANDA209190\0001\m5\datasets\rp-lid-pk001,
\\Cdsesub1\Evsprod\ANDA209190\0006\m5\datasets\rp-lid-ssi and
\\Cdsesub1\Evsprod\ANDA209190\0007\m5\datasets\rp-lid-ssi.

The data definition files are located at
\\Cdsesub1\Evsprod\ANDA209190\0001\m5\datasets\rp-lid-ssi,
\\Cdsesub1\Evsprod\ANDA209190\0001\m5\datasets\rp-lid-pk001 and
\\Cdsesub1\Evsprod\ANDA209190\0007\m5\datasets\rp-lid-ssi.

The clinical study reports, protocols and statistical reports are located at
\\Cdsesub1\Evsprod\ANDA209190\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\rp-lid-ssi and
\\Cdsesub1\Evsprod\ANDA209190\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\rp-lid-pk001.

Some SAS codes have been provided in the May 23, 2016 submission. They are located at

\\Cdsesub1\Evsprod\ANDA209190\0001\m5\datasets\rp-lid-ssi\analysis\legacy\programs and \\Cdsesub1\Evsprod\ANDA209190\0001\m5\datasets\rp-lid-pk001\analysis\legacy\programs.

3 STATISTICAL EVALUATION

The applicant submitted results from two studies - an irritation and sensitization study (Study RP-LID-SSI, titled "A Randomized, Controlled Study to Evaluate the Skin Irritation and Sensitization Potential of a Test Lidocaine 5% Topical Patch Compared to Lidoderm 5% Topical Patch Using a Repeat Insult Patch Test Design in Healthy Adults"), and a pharmacokinetic and adhesion study (Study RP-LID-PK001, titled "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults under Fasted Conditions"). This review is based on both studies.

3.1 Data and Analysis Quality

Study RP-LID-SSI

The quality of the submitted data and data definition in this application was extremely poor. The reviewer does not have confidence in the results due to the problems with the datasets. Here are the main issues with the datasets and related documents in the submission.

1. There were numerous inconsistencies within and between datasets. The datasets contained incomplete information and many errors. Some of the errors were revealed by the applicant only after FDA asked for information or clarification about inconsistencies in the datasets in Easily Correctable Deficiency (ECD) letters. There are likely many more undetected errors in the datasets. Following are some examples.
    a. The irritation and sensitizations analysis populations and reasons for exclusion from the analysis populations did not match between originally submitted datasets and the datasets submitted on December 9, 2016 in response to an ECD.
    b. The adhesion score for a detached patch should be 4 based on the adhesion scale used in the study. The patch detachment flag and adhesion score were not consistent in the dataset q4-oct16.xpt submitted on December 9, 2016 (please see Table 11).
    c. According to the original submission the test patch of Subject (b) (6) and the reference patches of Subjects (b) (6) detached during the challenge phase. However, as shown in Table 10, based on December 9, 2016 submission, the test patches of Subject (b) (6) and the reference patch of Subjec (b) (6) detached during the challenge phase. These conflicting data give an indication of a possibility of reversing the test and reference data for some or all subjects in the dataset. If that happened, all analyses would be wrong. This gives a strong reason why inconsistent data should never be considered for an approval.
    d. In the response to the statistical reviewer's request sent in an ECD letter, the applicant provided a list of patches that were detached and if a replacement patch was applied within 24 hours after detachment. The reviewer found out that for some subjects with detached patches in the list there was no information about detached patches in the data whereas the data contained the same information as the list for some other subjects. When the reviewer pointed it out in another ECD

letter to the applicant, the applicant agreed that the dataset did not have the correct information and resubmitted the patch adhesion dataset.

e. The reviewer asked for clarification about a discrepancy that the patch removal date and time did not match between ex.xpt and adph.xpt for some subjects. The applicant admitted the mistake and resubmitted the latter dataset.

2. Some data definition files did not have sufficient documentation and were not clear. Specifically, the variables AVAL and AVLC for each parameter in an ADaM dataset must be clearly defined. However, the data definition files did not have them. The applicant updated some data definition files in response to an FDA request for clarification of those variables for all parameters.

3. The information provided in some ECD responses was wrong or incomplete. Following are some examples.
   a. In response to an ECD letter, the applicant submitted a list subjects with detached patches. However, the reviewer found out that there were subjects with detached patches in the dataset that were not included in the list. When the reviewer pointed it out in a subsequent ECD letter to the applicant, the applicant replied that the subjects who had not completed the study were not included in that list. It appears that the applicant assumed that only the subjects that they thought would be included in the primary analysis had useful information. This is contrary to the good clinical practice.
   b. The reviewer noticed that the list of detached patches that the applicant provided in response to an ECD letter included a subject with detached patches that did not have any detached patches according to the data. When the reviewer pointed it out in another ECD letter to the applicant, the applicant admitted that the subject was included in the list erroneously.

4. Some case report forms were not submitted. Also, the case report forms were not well organized, had many errors and had too many data clarification forms attached with duplicate pages or duplicate notes.

Study RP-LID-PK001

Overall data and analysis quality for this study was acceptable.

3.2 Evaluation of Study RP-LID-SSI (Irritation and Sensitization Study)

3.2.1 Study Objectives

The primary objectives of this study were:

- To evaluate the skin irritation induced by topical application of the test lidocaine 5% patch compared to Lidoderm 5% lidocaine patch following 21 days of exposure in healthy adult male and female subjects.

- To evaluate the skin sensitization induced by topical application of the test lidocaine 5% patch compared to Lidoderm 5% lidocaine patch after a 21-day induction phase, followed by a 48-hour challenge phase in healthy adult male and female subjects.

The secondary objective of this study was:

- To assess the safety and tolerability of a test lidocaine 5% topical patch compared to Lidoderm 5% lidocaine patch in healthy adult male and female subjects.

3.2.2 Study Design

This was a randomized, single-center, controlled, evaluator-blinded study to evaluate the potential for skin irritation and sensitization of a test lidocaine 5% transdermal patch compared to the reference Lidoderm® 5% lidocaine patch in healthy adult subjects.

The test and reference products were the following.

- Test Patch: The test formulation of lidocaine 5% topical patch (distributed by Rhodes Pharmaceuticals L.P., and manufactured by Altergon, Italia).
- Reference Patch: Lidoderm® (lidocaine patch 5%) (manufactured b (b) (4) for Endo Pharmaceuticals, Inc.)

All applications of test and reference study product consisted of one-fourth of the patch.

The study had two phases:

- Skin irritation was assessed during the induction phase (Days 1-22)
- Skin sensitization was assessed during the challenge phase (Days 36-41)

Irritation/Induction Phase (Days 1-22):

During the induction phase, study products were applied simultaneously to the same sites on one side of the infrascapular area of the back of each subject. Study products were replaced 3 times weekly (for example, Mondays, Wednesdays, Fridays, or Tuesdays, Thursdays and Saturdays) at the same site for 3 consecutive weeks resulting in a total of 9 applications. The test and reference products for each subject were randomly assigned to application sites designated as “upper” and “lower” indicating the relative positioning of the patches to each other. The randomization scheme is shown in Table 1.

Table 1: Randomization Scheme for Study RP-LID-SSI

Randomization sequence	Test patch site	Reference patch site
1	Upper	Lower
2	Lower	Upper

Following removal of each patch and prior to patch replacement, the patch site was clinically assessed for dermal response in a blinded manner using a visual scale of 0-7 that rated the degree of erythema, edema and other features indicative of irritation. Other effects were rated on a visual scale of 0-6. The total of these scores (0-13) for each patch was considered the irritation score of each patch at each evaluation time point. Patch adhesion data, based on a visual scale of 0-4 as described in Section 3.2.3, was collected prior to removal of each patch.

If a patch was removed for an unacceptable degree of irritation, and a new patch could not be applied to the same site, subsequent applications of the product could be applied to a different skin site on the back (on the same side of the spine) in order to complete the induction phase. The highest score observed prior to patch discontinuation was to be carried forward for all remaining observations. Up to two changes in patch application site could occur. If a third patch was removed for an unacceptable degree of irritation, the subject was to be excluded from both the irritation and sensitization analyses of the product, and discontinued from study participation.

If a patch completely detached, it was to be replaced within 24 hours and the subject would continue in the study. Subjects were to note the date and time of detachment as soon as it occurred. If a patch could not be replaced within 24 hours, or a subject did not know when a patch detached, the subject was to be excluded from both the irritation and sensitization analyses of that product, and was to be discontinued from study participation.

If patch adhesion was assessed as <50% adhered but not detached (more than half the system lifting off of the skin without falling off), the subject was scheduled for a make-up patch application. The skin irritation assessments for the patches that adhered <50% were not to be included in the irritation analyses.

Subjects who did not return for one visit to the study site during the induction phase were instructed to keep the patches in place. They were scheduled to receive a make-up patch application at the last visit during the induction phase. The make-up patches were removed 48 hours later and the patch sites were assessed. If subjects failed to return for removal/evaluation of the make-up patches, the ninth assessment was not recorded. A subject who missed the ninth assessment but had 9 patch applications was considered to have completed the induction phase, and the last observation was carried forward.

The induction phase was followed by a 12- to 14-day rest phase, and then a challenge phase.

Sensitization/Challenge Phase (Days 36-41):

Subjects who completed the induction phase and the rest phase had the test and reference products applied to naïve sites for 48 hours. The site of application (“upper” or “lower”) was the same as that used during the induction phase but on the other side of the spine. Subjects returned to the study site after 48 hours of patch wear to have the patches removed. Prior to removal of

each patch, patch adhesion was assessed based on a visual scale of 0-4 as described in Section 3.2.3.

The patch site was clinically assessed 30 minutes and 24, 48 and 72 hours after patch removal for dermal response and other effects scores in the same manner as in the induction phase. A narrative description of each reaction during the challenge phase was provided by the investigator, along with an opinion as to whether such reactions were thought to be indicative of contact sensitization.

If study product was removed prior to 48 hours of patch wear due to a sensitization reaction, the last observation was carried forward.

Subjects were questioned about itching, burning, pain or soreness at the application site. These symptoms were recorded and compared between products. Concomitant medications and adverse events were recorded and reviewed at each visit to the study site.

Whereas bathing was allowed (low tub bath/frontal showers), the patched area was not to be soaked and was to be kept as dry as possible, per instructions to each subject. Subjects could not use systemic or topical analgesics, corticosteroids or nonsteroidal anti-inflammatory drugs within 3 weeks prior to first study product application; or systemic or topical antihistamines within 72 hours prior to first study product application. The use of make-up, creams, lotions, powders or other topical products to the skin area where patches were applied was prohibited. Subjects refrained from excessive physical activity or exercise that could cause perspiration.

Patch application, patch removal and assessment of patch adhesion were not performed in a blinded manner since the test and reference patches had different appearances. Irritation analyses were performed in a blinded manner by the investigator. This was accomplished by having patch application, patch removal and adhesion assessment performed in one room by staff not involved in irritation analysis, and skin irritation performed in a separate room.

Reviewer's Comments:

1. According to the protocol, if three patches of a subject were moved or removed for unacceptable degree of irritation during the induction phase, the subject was to be excluded from both the irritation and sensitization analyses of the product, and discontinued from study participation. However, FDA guidance recommends including those subjects in the irritation analysis using last observation carried forward (LOCF). No subject was discontinued due to excessive irritation in this study.

2. According to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion score of 3) during the induction phase, the skin irritation assessment for that patch was not to be included in the irritation analysis and the subject was to be scheduled for a make-up patch application. It is understood that the irritation score from a make-up patch would replace the irritation score of the patch that was <50% adhered but not detached if only a single patch out of 9 patches had <50% adherence without being

detached. However, the protocol did not state how the irritation scores would be used when two or more patches of the same type for the same person had <50% adherence without being detached. In response to an ECD (ECD letter date: September 16, 2016, ECD response date: September 29, 2016), the applicant stated that when there were multiple patches of the same type with an adhesion score of 3 for the same subject, a single make-up patch was applied and the irritation score for the make-up patch replaced the irritation scores of all the patches with an adhesion score of 3 that the make-up patch replaced. The applicant adjusted the number of irritation assessments by counting the number of patches not having an adhesion score of 3 and adding one for the make-up patch to that count. For example, if there are 3 patches with an adhesion score of 3, then the number of irritation scores used to calculate the mean would be 6+1=7. In the reviewer's opinion, this is not an appropriate method to calculate the mean irritation score since it essentially reduces the number of irritation scores unless there is only one patch with an adhesion score of 3. The particular patch type for that subject should be excluded from the irritation and sensitization analyses.

3. The study design did not follow the Draft Guidance on Lidocaine. According to the guidance, patches should be applied on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the induction phase. The patches should be assessed for irritation after patch removal and before new patch application. Patches applied on Day 19 should be assessed on Day 22. Based on the protocol, the subjects were allowed to skip a visit and keep the patches on until the next visit when they were evaluated for skin irritation. It resulted in having the same patch on for 4 or 5 days before an irritation assessment while the patches without a skipped visit were on for 2 or 3 days before the irritation assessment.

4. According to the protocol, the subjects who did not return for one visit to the study site during the induction phase were instructed to keep the patches in place. They were scheduled to receive a make-up patch application at the last visit during the induction phase. The study report did not clearly differentiate the dual use of the terminology "make-up patch" for two different purposes. In the first case the make-up patch is intended to replace the irritation score of a partially detached (<50% adhesion but not completely detached) patch. In the second case, the irritation score of the make-up patch is simply intended to be an additional patch when a visit was skipped to make a total of 9 patches during the induction phase.

5. According to the protocol, a subject who missed the ninth assessment but had 9 patch applications was considered to have completed the induction phase, and the last observed irritation score (the irritation score for the eighth patch) was carried forward. This approach contradicts the Draft Guidance on Lidocaine since the guidance requires application and evaluation of all 9 patches unless the patch removal is due to excessive irritation. In the reviewer's opinion the subjects who missed the ninth assessment should be excluded from the irritation and sensitization analyses.

6. The protocol specified that hypoallergenic tape would be applied to all four edges of each patch. However, there was no mention of this reinforcement tape in the clinical study

report. In response to an ECD (ECD letter date: August 23, 2016, ECD response date: September 6, 2016), the applicant confirmed that the hypoallergenic tape was used on all four edges and diagonally on all patches.

3.2.3 Assessments

Both irritation and sensitization were assessed based on the following rating scales given in Table 2 and Table 3:

Table 2: Dermal Response Rating Scale

Score	Skin Appearance
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible, or minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond the application site

Table 3: Applicant's "Other Effects" Rating Scale

Score	Observation
1	Slightly glazed appearance
2	Marked glazed appearance
3	Glazing with peeling and cracking
4	Glazing with fissures
5	Film of dried serous exudates covering all or part of the patch site
6	Small petechial erosions and/or scabs
0	No other observations

Skin Irritation Assessments

Following removal of each patch and prior to patch replacement, the patch site was clinically assessed for dermal response and other effects in a blinded manner using the above rating scales.

At each assessment time point for each subject, for each product, an irritation score (IS) was calculated by adding the dermal response score to the other effects score.

Skin Sensitization Assessments

Sensitization assessments of the site of each patch application were made approximately 30 minutes and 24, 48 and 72 hours after patch removal in the challenge phase. The same rating scales as used during the induction phase were used. A narrative description of each reaction during the challenge phase was provided by the investigator, along with an opinion as to whether such reactions were thought to be indicative of contact sensitization.

Adhesion Assessment

Patch adhesion was assessed prior to patch removal by qualified study site personnel. The following adhesion scale was used to record a score for each individual patch.

0 = ≥ 90% adhered (essentially no lift off the skin)
1 = ≥ 75% to <90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to <75% adhered (less than half of the patch lifting off the skin)
3 = >0% to < 50% adhered but not detached (more than half of the patch lifting off the skin but not completely detached)
4 = 0% adhered - patch detached (patch completely off the skin)

Due to the differences in appearance of the patches, blinding of the evaluator for patch adhesion was not possible.

If patch adhesion was assessed as <50% adhered but not detached (more than half the patch lifting off the skin without falling off), the subject was scheduled for a make-up patch application. The skin irritation assessment for the patch adhered < 50% was not included in the irritation analyses.

Reviewer's Comment:

The applicant used a different rating scale for "other effects" than what is recommend by FDA in Draft Guidance on Lidocaine. Although the other effects categories are identical between the applicant's and FDA's scales, the numerical values associated with the categories based on the applicant's scale are higher with a wider range than those based on the FDA's scale. The applicant did not use any letter score for the other effects. The other effects rating scales based on the applicant and FDA are presented side by side in Table 4. The applicant's other effects rating scale increases the irritation score (dermal response score + other effects score). This increased irritation score makes both the numerator and denominator of the test statistic, which is a ratio (Test/Reference), larger and thus the ratio closer to one numerically. Therefore, the test is more likely to be found non-inferior to the reference with the applicant's rating scale. The reviewer used the FDA-recommended scale for the analyses of irritation and sensitization.

Table 4: Comparison of Applicant's and FDA's "Other Effects" Rating Scales

Applicant's Scale	FDA's Scale		Observation
	Letter Score	Numeric Score	
0	N	0	No observation
1	A	0	Slightly glazed appearance
2	B	1	Marked glazed appearance
3	C	2	Glazing with peeling and cracking
4	F	3	Glazing with fissures
5	G	3	Film of dried serous exudates covering all or part of the patch site
6	H	3	Small petechial erosions and/or scabs

3.2.4 Changes in the Study Conduct

The induction phase for Cohort 2 was shortened by one day (total 20 instead of 21 per protocol). The patch application schedule for the induction phase for Cohort 2 of this study was Tuesday, Thursday and Saturday and the first patch application of all subjects in this cohort was Tuesday, November 5, 2013. This schedule meant that the last dose application for the induction phase would be on Saturday, 23 November 2013 and the last skin assessment would be on Tuesday November 26, 2013. If subjects required a make-up patch application, this would occur on the latter date and the subsequent skin assessment would be on Thanksgiving, Thursday, 28 November 2013, requiring subjects to return to the clinic on Thanksgiving for this assessment. Due to the concern regarding potential subject compliance, a decision was made to have the last scheduled skin assessment and make-up patch applications, if required, for Monday, 25 November 2013 instead of Tuesday, 26 November 2013 to avoid this conflict. This change was documented in a note to file (dated 11 February 2014).

Reviewer's Comment:

According to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion score of 3) during the induction phase, the skin irritation assessment for that patch was not to be included in the irritation analysis and the subject was to be scheduled for a make-up patch application. The protocol did not state if a make-up patch would be applied for the patches that completely detached (adhesion score of 4). The data and an inspection report by the Office of Study Integrity and Surveillance (OSIS) revealed that make-up patches were applied for subjects who did not have any patch adhesion score of 3. The OSIS report noted that the study was not conducted according to the investigational plan. The OSIS report indicated that there were 12 subjects (Subject ID (b) (6) who had completely detached patches (adhesion score of 4). The reviewer found more such cases (please refer to Table 9).

3.2.5 Study Endpoints

3.2.5.1 Applicant's Endpoints

Primary endpoints:

- Dermal response scores and scores for other effects collected during the induction phase to evaluate the skin irritation potential of the study product.
- Dermal response scores and scores for other effects collected during the challenge phase to evaluate the skin sensitization potential of the study product.
- The number of patches removed due to an unacceptable degree of irritation.
- The number of days until sufficient irritation occurs to preclude patch application.

Secondary endpoint:

- The incidence of treatment-emergent adverse events, including itching, burning, pain or soreness at the application site, and study discontinuation information.

3.2.5.2 Reviewer's Endpoints

In the following definitions, the irritation score for a patch is calculated as the sum of dermal response and numeric other effects scores based on the FDA's recommended scoring of these two items as shown in Table 2 and Table 4.

Primary endpoint for irritation:

The reviewer' primary endpoint for irritation is the mean irritation score which is defined for a patch type for a subject as the mean of irritation scores observed after removal of each of the 9 patches of that patch type for that subject during the induction phase. If a patch is discontinued due to excessive irritation, the last observed score is carried forward for the rest of the induction phase before calculating the mean irritation score.

Secondary endpoints for irritation:

- The proportion of subjects with a meaningful degree of irritation (irritation score ≥ 3 at any time point)
- The time to patch discontinuation for excessive irritation (irritation score ≥ 3).

Primary endpoint for sensitization:

Irritation scores at 48 and 72 hours after patch removal during the challenge phase.

3.2.6 Sample Size Considerations

The applicant targeted a sample size of 200 evaluable subjects based on the industry and regulatory standards for determination of dermal sensitization potential. In the absence of any sensitization reactions, a 95% upper confidence boundary on the population rate of sensitization would be 1.5%. Approximately 250 subjects were enrolled and randomized in order to have 200 evaluable subjects complete the study.

3.2.7 Statistical Methodologies

3.2.7.1 Analysis Populations

Applicant's Analysis Populations:

Test Irritation Analysis Population:

The Test Irritation Analysis Population includes all subjects who received all test patches such that sequential test patch applications were not detached from the skin for longer than 24 hours during the 21-day induction Phase (unless the patch was removed for an unacceptable degree of irritation). If a test patch detached and could not be replaced within 24 hours, or a subject did not know when a test patch detached, the subject's test patch was to be excluded from the Test Irritation Analysis Population.

Reference Irritation Analysis Population:

The Reference Irritation Analysis Population is defined for reference patches in a similar way to the Test Irritation Analysis Population.

Full Irritation Analysis Population:

The Full Irritation Analysis Population includes all subjects who were in both the Test Irritation Analysis Population and the Reference Irritation Analysis Population. The Full Irritation Analysis Population was used for all irritation analyses requiring paired test/reference irritation data.

Test Sensitization Analysis Population:

The Test Sensitization Analysis Population includes all subjects who received test patches (challenge phase) and who have completed the induction phase, wearing the test patches for the entire 21 days and completed the rest phase. Additionally the challenge test patch must be attached for 48 hours (unless the challenge test patch was removed due to a sensitization reaction) with the subject returning for evaluation at least 24 hours after removal of the challenge test patch.

Reference Sensitization Analysis Population:

The Reference Sensitization Analysis Population is defined for reference patches in a similar way to the Test Sensitization Analysis Population.

Full Sensitization Analysis Population:

The Full Sensitization Analysis Population includes all subjects who were in both the Test Sensitization Analysis Population and the Reference Sensitization Analysis Population. The Full Sensitization Analysis Population was used for all sensitization analyses requiring paired test/reference sensitization data.

Safety Population:

All subjects who received at least one application of either study product were included in the Safety Population.

FDA's Analysis Populations:

Per protocol population for irritation (PPPI):

The PPPI consists of patch types for the subjects who had the study products applied sequentially to the same site for the entire 21 day induction phase (without any period of detachment longer than 24 hours) to be evaluated for the cumulative irritation effect, or if a patch is moved or removed due to excessive irritation. In the event that a patch was moved or removed due to excessive irritation, the last observed score prior to discontinuation of the first patch site is carried forward for all remaining observations in the irritation analysis.

Per protocol population for sensitization (PPPS):

The PPPS consists of patch types for the subjects who have worn the study products (without any period of detachment longer than 24 hours) for the full 21-day induction phase and the entire 48-hour challenge phase and have returned for at least one of the scheduled evaluations at 48 and 72 hours after removal of the challenge patch. If a study product is removed prior to the end of the 48-hour challenge phase due to an intolerable reaction, the application site should be evaluated at 24, 48, and 72 hours after patch removal and included in the sensitization analysis using the last observation carried forward (LOCF).

Safety population (SP):

All subjects who had at least one patch applied were included in the safety population.

Reviewer's Comments:

1. The FDA's PPPI defined above and the combined collection of test patches from the subjects in the applicant's test irritation analysis population and the reference patches from the subjects in the reference irritation analysis population are same. However, the applicant did not specify how the missing observations will be handled when the patches are removed due to excessive irritation. In this study no patch was removed due to excessive irritation.

2. The FDA's PPPS is almost same as the combined collection of patches in the applicant's test sensitization analysis population and the reference sensitization analysis population except that PPPS has an extra requirement of the challenge phase patches to be evaluated at least once at or after 48 hours after patch removal.

3.2.7.2 Analysis of Irritation

Applicant's Analysis Methods:

The irritation score (0-13) for each study product at each evaluation was the sum of the dermal response score (0-7) and the score for other effects (0-6). The cumulative irritancy index (CII) was defined as the mean of irritation scores across all assessments during the induction phase. The cumulative dermal response index and the cumulative other effects index were also defined similarly. All these three indexes were generated for test and reference study product for each subject and summarized by treatment and by cohort. The individual CIIs, the individual cumulative dermal response index and the individual cumulative other effects index generated during the induction phase were tested for product differences using the 2-way analysis of variance (ANOVA) including main effects of subject and product, without interaction using the PROC GLM model. The test product was to be no more irritating than the RLD, as defined by the upper bound of the one-sided 95% confidence interval of the difference between the products being no greater than 0.11.

Individual CIIs generated during the challenge phase were summarized by treatment and by cohort. A frequency table displayed the number of applications of each study product with each irritation score at each evaluation time point by treatment and by cohort. Subjects' maximum irritation score, maximum dermal response score, maximum other effects score, total number of observations with a maximum irritation score of 13, a maximum dermal response score of 7, a maximum other effects score of 6 and the number of patches that were removed due to an unacceptable degree of irritation were summarized by treatment, cohort, time point and overall.
The statistical comparisons of the test and reference products in each cohort and overall for total number of observations with a maximum irritation score and the number of patches that were removed were performed using McNemar's test on the Full Irritation Analysis Population.

The number of days until sufficient irritation occurred to preclude patch application, was calculated and summarized for the test and reference study products and cohort. The statistical

comparison of the test and reference products, overall and within each cohort, was performed using the Kaplan-Meier test using the SAS procedure PROC LIFETEST. A Kaplan-Meier curve was generated by treatment for overall and within each cohort on the Full Irritation Analysis Population.

If a patch was removed for an unacceptable degree of irritation and a new patch could not be applied to the same site, the highest score observed prior to patch discontinuation was carried forward for all remaining observations. Subsequent applications of the product were applied to a different skin site in order to complete the Induction Phase. Subjects were required to have a minimum of 9 patch applications during the Induction Phase.

Reviewer's Primary Analysis Method:

For the primary analysis of the primary endpoint, an analysis of variance (ANOVA) was performed in which the mean irritation score was treated as the dependent variable, and subject and treatment were treated as fixed effects.

Reviewer's Method for the Analysis of the Binary Endpoint:

The binary endpoint, the number of subjects with a meaningful degree of irritation (≥ 3) is analyzed in the PPPI.

The objective is to test a non-inferiority hypothesis as follows:

$$H_0: P_T - P_R > \delta \text{ (not non-inferior)}$$

$$H_1: P_T - P_R \leq \delta \text{ (non-inferior),}$$

where P_T and P_R are the proportions of clinically significant irritation or sensitization ("event") for TEST and RLD, and δ is a pre-specified non-inferiority margin. The significance level is 0.05. Non-inferiority is established if the upper bound (UB) of the one-sided 95% confidence interval of $P_T - P_R$ is less than or equal to δ. The tabulation of event/non-event for Test and RLD is as follows.

Total n=a+b+c+d		Test	
		Non-Event	Event
RLD	Non-Event	a	b
	Event	c	d

Let
n = total number of subjects;
b = number of subjects with a negative outcome (irritation, sensitization or detachment) using the test but not the comparator;
c = number of subjects with a negative outcome (irritation, sensitization or detachment) using the comparator but not the test.

The matched proportion difference $P_T - P_R$ can be estimated by the quantity $\frac{b-c}{n}$ after a simple derivation. There are different ways to calculate the upper bound of the matched proportion difference $P_T - P_R$. A common way is to use the McNemar method[1] based on normal approximation under the law of large numbers. The UB is calculated as follows:

$$UB = \frac{b-c}{n} + 1.645\frac{1}{n}\sqrt{b+c-\frac{(b-c)^2}{n}}$$

Schuirmann[2] proposed a different way of normal approximation by combining Nam's[3] and Liu et al's[4] approaches. Based on the simulation results, Schuirmann[2] recommended an optimal normal approximation which preserves better type I error for smaller rates compared to McNemar method.

$$\text{Let } Z = \frac{\hat{\delta} + cc - \delta}{\sqrt{\frac{\xi^* - \delta^2}{n}}},$$

where $\hat{\delta} = \frac{b-c}{n}$, the continuity correction, $cc = \frac{1}{n}$, $\xi^* = \max(\hat{\delta}, |\delta|)$.

The one-sided 95% upper bound (UB) for the matched proportion difference, $P_T - P_R$, is the value of δ that makes $Z = Z_{0.05} = -1.64$. Schuirmann's method was used in this statistical report. For any given non-inferiority bound δ, the null hypothesis H_0 may be rejected if this 95% upper confidence bound for the quantity $P_T - P_R$ is less than or equal to δ, that is: $U \leq \delta$. Rejection of the null hypothesis H_0 supports the conclusion of non-inferiority of the test to the comparator.

3.2.7.3 Analysis of Sensitization

Applicant's Analysis Methods:

Sensitization of test versus reference study product was based on irritation scores obtained during the challenge phase and whether the reactions were indicative of a sensitization reaction by the investigator.

A skin sensitization reaction was defined as the development, at the site of re-exposure to the patch, of definite erythema combined with the presence of any of the following signs: papules, edema, vesicles, bullae, cracking, fissuring, crusting, peeling, or spread beyond the confines of patch application site. Such reactions were required to have a time course compatible with a

sensitization reaction; that is, such a reaction occurring at the beginning of the induction phase would be deemed a sign of prior sensitization, and reactions which markedly improved within a 72-96 hour timeframe were not characteristic of allergic response, and were classified as an irritant response. Skin sensitization reactions would most likely occur in the challenge phase, although they could occur later in the induction phase, and would have a time course characteristic of Type IV delayed hypersensitivity reactions.

Sensitization by time point was summarized using number and percentage and tested for product differences using McNemar's test. If the study product was removed prior to 48 hours due to a sensitization reaction, the last observation was carried forward and the subject was included in the sensitization analysis.

Reviewer's Analysis Methods:

The Draft Guidance on Lidocaine states the following:

For each test article, individually evaluate each PP subject with a combined score of 2 or greater at 48 or 72 hours after patch removal during the challenge phase for potential sensitization. A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. Consider a subject to be potentially sensitized if all of the following criteria are met:

a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the challenge phase patch.
b. The subject has a combined "dermal response" and "other effects" numeric score of at least 2 at their last evaluation during the challenge phase.
c. The combined "dermal response" and "other effects" numeric scores obtained during the challenge phase evaluations are generally higher than the combined "dermal response" and "other effects" numeric scores obtained during the induction phase.
d. If the subject completed a rechallenge phase, the above 3 criteria were met during both the challenge phase and the rechallenge phase.

FDA's determination of sensitization used the recommendations provided in the guidance.

The reviewer's method for analysis of sensitization is same as that for the analysis of binary endpoint described earlier.

3.2.7.4 Analysis of Adhesion

Due to the differences in appearance of the patches, blinding of the evaluator for patch adhesion was not possible. If patch adhesion was assessed as <50% adhered but not detached (more than half the system lifting off of the skin without falling off), the subject was scheduled for a make-

up patch application. The skin irritation assessment for the patch adhered < 50% was not included in the irritation analyses.

Adhesion data for each study product was collected and displayed to document that adhesion of the study product was adequate for the skin irritation and sensitization analyses. Adhesion scores from all patches within each treatment were summed and divided by the number of scores to calculate a cumulative adhesion index for each subject by cohort. No statistical tests were performed on adhesion data. Total number of patch detachments, per subject, of each study product in induction phase was summarized overall and by cohort for the full irritation analysis population.

3.2.8 Subject Disposition and Analysis Populations

A total of 248 healthy adult subjects were entered into this study and received at least one application of patches. All subjects were included in the safety population.

Subjects were dosed in two cohorts. All subjects in the first cohort had the first patch application on August 20, 2013 and the subjects in the second cohort had the first patch application on November 5, 2013. The first and the second cohorts had 123 and 125 subjects, respectively.

The PPPI and PPPS refer to the per protocol population for irritation and per protocol population for sensitization, respectively. Although the applicant did not use these terminologies in the protocol or the study report, it should be noted that the FDA's PPPI is same as the combined collection of test patches from the subjects in the applicant's test irritation analysis population and the reference patches from the subjects in the applicant's reference irritation analysis population. The same is nearly true for PPPS. Please refer to Section 3.2.7.1 for more details.

The FDA reviewer considered six different PPPIs and six different PPPSs due to issues with the design and conduct of the study and inconsistent data. These populations are named as PPPI1, PPPI2, etc. and PPPS1, PPPS2, etc., respectively. PPPI1 and PPPS1 are the largest populations. All other PPPIs are subsets of PPPI1 and all other PPPSs are subsets of PPPS1. In this and later sections FDA's PPPI and FDA's PPPS will mean PPPI1 and PPPS1, respectively unless otherwise stated.

3.2.8.1 Applicant's Subject Disposition and Exclusion from Analysis Populations

Four subject (b) (6) withdrew from the study during the induction phase. For these sub excluded from the PPPI and PPPS by the applicant in the originally submitted data and by the FDA reviewer. In the dataset submitted on December 9, 2016, these subjects were excluded from the PPPI but included in the PPPS without any explanation.

Subjec (b) (6) did not have any patch applications after the fourth set of patches, Subject (b) (6) did not have any patch applications after the fifth set of patches, Subject (b) (6) did not have any patch applications after the first set of patches, Subjec (b) (6) did not have any patch applications after the sixth set of patches and Subjects (b) (6) did not have any patch applications after the second set of patches during the induction phase. Both patch types of these subjects were excluded from the PPPI and PPPS by the applicant and the FDA reviewer.

Subjects (b) (6) did not have the skin irritation assessment on Da (b) (6) for the first set of patches during the induction phase. The applicant excluded both patch types for Subject (b) (6) from the PPPI and from the PPPS and included both patch types for the Subject (b) (6) in the PPI and PPPS in the dataset submitted on December 9, 2016. Both patches for Subject (b) (6) and the reference patch for Subject (b) (6) were included in the PPPS in the originally submitted data. After reviewing the case report forms the FDA reviewer excluded these patches from both PPPI and PPPS.

Subjec (b) (6) did not have the skin irritation assessment on Day (b) (6) for the second set of patches during the induction phase and Subjec (b) (6) did not have the skin irritation assessment on Day (b) (6) for the fifth set of patches during the induction phase. The applicant excluded both patch types for these subjects from the PPPI but included them in the PPPS in the originally submitted data. The applicant included them in both PPPI and PPPS in the dataset submitted on December 9, 2016. After reviewing the case report forms the FDA reviewer excluded both patch types for Subjects (b) (6) from both PPPI and PPPS.

Subject (b) (6) completed the induction phase but was discontinued from the study by the investigator before the challenge phase because the principal investigator decided that it was in the subject's best interest. The applicant included both patch types for the subject in the PPPI in the originally submitted data but excluded from the PPPI in the dataset submitted on December 9, 2016. After reviewing the case report form, the FDA reviewer decided to include both patch types for the subject in the PPPI. Both patch types of the subject were excluded from the PPPS by the applicant in the originally submitted dataset and by the FDA reviewer. However, both patch types were included in the PPPS by the applicant in the dataset submitted on December 9, 2016.

Subject (b) (6) was discontinued due to concomitant medication. The case report form for the subject was not submitted. Based on the dataset, no more patches after the third patch were applied during the induction phase for this subject. Therefore, both patch types for this subject was excluded from the PPPI by the applicant and the FDA reviewer.

Subjec (b) (6) completed the induction phase but did not participate in the challenge phase due to hospitalization before the challenge phase. Protocol deviation due to use of restricted medication occurred after the completion of the induction phase but before the challenge phase. The applicant included both patch types for the subject in the PPPI in the originally submitted data but excluded them from the PPPI in the dataset submitted on December 9, 2016. After reviewing the case report form, the FDA reviewer decided to include both patch types for the subject in the

PPPI. Both patch types of the subject were excluded from the PPPS by the applicant and the FDA reviewer.

Subjec (b) (6) completed the induction phase and started the challenge phase but did not have any skin irritation assessments due to hospitalization. Protocol deviation due to use of restricted medication occurred during the challenge phase. The applicant included both patch types for the subject in the PPPI in the originally submitted data but excluded from the PPPI in the dataset submitted on December 9, 2016. After reviewing the case report form, the FDA reviewer decided to include both patch types for the subject in the PPPI. Both patch types of the subject were excluded from the PPPS by the applicant and the FDA reviewer.

Subject (b) (6) did not have the eighth and ninth patch applications and also skin irritation assessment was not performed for the seventh patch during the induction phase. The subject was hospitalized on Da (b) (6) of the induction phase and took medication prohibited by the protocol. The reason for early termination in the case report form is given as non-compliance with the protocol. Both patch types for this subject were excluded from the PPPI and PPPS by the applicant and the FDA reviewer.

Subject (b) (6) skipped the Da (b) (6) visit during the induction phase. For this subject, the skin irritation on Da (b) (6) and Day (b) (6) were assessed 1 and 2 minutes outside the window, respectively, during the induction phase based on the comments in the protocol deviation section of the case report form. In the challenge phase, 24 hours post-application skin irritation assessment was collected 82 minutes out of the window and 72 hours post-application assessment was not done. The applicant included both patch types for the subject in the PPPI and PPPS in the originally submitted data but excluded from the PPPI and PPPS in the dataset submitted on December 9, 2016. The irritation assessments on Da (b) (6) and Da (b) (6) were done 9 and 8 minutes, respectively, after patch removal. According to the protocol (Section 4), skin irritation assessments were to occur within 15-30 minutes following removal of each patch during induction phase. Therefore, the comments about out-of-window irritation assessments during the induction phase in the CRF are not consistent with the protocol. The out-of-window assessment at 24 hours and the missing assessment at 72 hours after patch removal during the challenge phase did not affect the eligibility of the challenge patches to be included in the PPPS. After reviewing the case report form, the FDA reviewer decided to include both patch types for the subject in the PPPI and PPPS. However, these patches were excluded from some of the irritation and sensitization analyses (when using PPPI2, PPPI4, PPPI6, PPPS2, PPPS4 and PPPS6) by FDA due to a skipped visit (please refer to Table 8).

The challenge phase patches for Subject (b) (6) were removed before 44 hours after application. The applicant excluded both patches of this subject from PPPS in the originally submitted data but included them in the PPPS in the dataset submitted on December 9, 2016. After reviewing the case report form the FDA reviewer excluded these patches from the PPPS. Both patch types for this subject were included in the PPPI by the applicant and the FDA reviewer.

The reference patch for Subject (b) (6) and both patches for Subjec (b) (6) in the challenge phase detached prior to 48 hour after application and the detachment time was

unknown. These patches were excluded from the PPPS by the applicant in the originally submitted dataset but included in the PPPS in the dataset submitted on December 9, 2016. After reviewing the case report form the FDA reviewer excluded these patches from the PPPS. Both patch types for these subjects were included in the PPPI by the applicant and the FDA reviewer. However, some patches of Subject (b) (6) detached during the induction phase (refer to Table 9). Replacement patches were applied within 24 hours after detachment in the case of Subjec (b) (6)

A side-by-side comparison of the subjects with at least one excluded patch from PPPI in either the applicant's original submission or the applicant's December 9, 2016 submission along with the reasons for exclusion is presented in Table 5. A similar comparison for PPPS is presented in Table 6. A comparison of the applicant's and FDA's determination about inclusion and exclusion of patches in PPPI and PPPS for the subjects with at least one patch excluded from PPPI or PPPS in at least one of the two submissions mentioned above is presented in Table 7.

Table 5: Comparison of Excluded Patches from the Applicant's PPPI Between the Original Submission and the December 9, 2016 Submission

Subject ID	Original submission		December 9, 2016 Submission	
	Excluded from PPPI (Both Patches)	Reason for exclusion form PPPI	Excluded from PPPI (Both Patches)	Reason for exclusion form PPPI
(b) (6)	Y	Subject didn't receive all patches	Y	1. A need for a concomitant medication prohibited by the protocol arises 2. Restricted medication
	N		Y	1. Adverse events 2. Restricted medication
	Y	Subject didn't receive all patches	Y	Voluntary withdrawal
	Y	Subject didn't receive all patches	Y	Voluntary withdrawal
	N		Y	The principal investigator decided that it is in the subject's best interest
	Y	Subject didn't receive all patches	Y	Non-compliant
	Y	Subject didn't have a minimum of 9 irritation scores during Induction Phase	Y	Non-compliant
	Y	Subject didn't receive all patches	Y	1. Non-compliant 2. Non-compliant

(b) (6)				
	Y	Subject didn't have a minimum of 9 irritation scores during Induction Phase	Y	Non-compliant
	Y	Subject didn't have a minimum of 9 irritation scores during Induction Phase	N	
	N		Y	Non-compliant
	Y	Subject didn't have a minimum of 9 irritation scores during Induction Phase	N	
	Y	Subject didn't receive all patches	Y	1. Non-compliant 2. Non-compliant
	Y	Subject didn't receive all patches	Y	1. Non-compliant 2. Non-compliant
	Y	Subject didn't have a minimum of 9 irritation scores during Induction Phase	N	
	Y	Subject didn't receive all patches	Y	1. Non-compliant 2. Non-compliant
	N		Y	1. Adverse events 2. Restricted medication
	Y	Subject didn't receive all patches	Y	1. Adverse events 2. Restricted medication
	Y	Subject didn't receive all patches	Y	1. Non-compliant 2. Patch-free >24 hr
	Y	Subject didn't receive all patches	Y	1. Non-compliant 2. Non-compliant
	Y	Subject didn't receive all patches	Y	Voluntary withdrawal
	Y	Subject didn't receive all patches	Y	1. Non-compliant 2. Non-compliant
	Y	Subject didn't receive all patches	Y	Voluntary withdrawal
	Y	Subject didn't receive all patches	Y	1. Not eligible 2. Other

Y=Yes, N=No; Mismatches are highlighted green (included in the PPPI in the original submission but excluded from the PPPI in the December 9, 2016 submission) and yellow (excluded from the PPPI in the original submission but included in the PPPI in the December 9, 2016 submission)

Table 6: Comparison of Excluded Patches from the Applicant's PPPS Between the Original Submission and the December 9, 2016 Submission

Subject ID	Patch Type	Original submission		December 9, 2016 Submission	
		Excluded from PPPS	Reason for exclusion form PPPS	Excluded from PPPS	Reason for exclusion form PPPS
(b) (6)	T, R	Y	Patch attached less than 44 Hrs	N	
	T, R	Y	Subject didn't complete Induction Phase	Y	1. A need for a concomitant medication prohibited by the protocol arises 2. Restricted medication
	T, R	Y	Subject discontinued study prior to Challenge Phase	Y	1. Adverse events 2. Restricted medication
	T, R	Y	Subject didn't complete Induction Phase	N	
	T, R	Y	Subject didn't complete Induction Phase	N	
	T, R	Y	Patch detached and detachment time was unknown	N	
	T, R	Y	Subject discontinued study prior to Challenge Phase	N	
	T, R	Y	Subject didn't complete Induction Phase	Y	Non-compliant
	T, R	Y	Subject didn't return for evaluation at least 24 Hrs after removal of challenge patch	Y	Non-compliant
	T, R	Y	Subject didn't complete Induction Phase	Y	1. Non-compliant 2. Non-compliant
	T, R	N		Y	Non-compliant
	T	Y	Patch detached and detachment time was unknown	N	
	R	N		N	
	T, R	N		Y	Non-compliant

(b) (6)

T	N		N	
R	Y	Patch detached and detachment time was unknown	N	
T, R	Y	Subject didn't complete Induction Phase	Y	1. Non-compliant 2. Non-compliant
T, R	Y	Subject didn't complete Induction Phase	Y	1. Non-compliant 2. Non-compliant
T, R	Y	Subject didn't complete Induction Phase	Y	1. Non-compliant 2. Non-compliant
T, R	N	Subject didn't return for evaluation at least 24 Hrs after removal of challenge patch	Y	1. Adverse events 2. Restricted medication
T, R	Y	Subject didn't complete Induction Phase	Y	1. Adverse events 2. Restricted medication
T, R	Y	Subject didn't complete Induction Phase	Y	1. Non-compliant 2. Patch-free >24 hr
T, R	Y	Subject didn't complete Induction Phase	Y	1. Non-compliant 2. Non-compliant
T, R	Y	Subject didn't complete Induction Phase	N	
T, R	Y	Subject didn't complete Induction Phase	Y	1. Non-compliant 2. Non-compliant
T	N		N	
R	Y	Patch detached and detachment time was unknown	N	
T, R	Y	Subject didn't complete Induction Phase	N	
T, R	Y	Subject didn't complete Induction Phase	Y	1. Not eligible 2. Other

=No; Patch type: T=Test, R=reference; Mismatches are highlighted green (included in the PPPS in the original submission but excluded from the PPPS in the December 9, 2016 submission) and yellow (excluded from the PPPS in the original submission but included in the PPPS in the December 9, 2016 submission)

Table 7: Comparison of Excluded Patches from PPPI and PPPS Between Applicant's Submissions and FDA's Determination

Subject ID	Original submission				9 Dec 2016 Submission				FDA Determination			
	Excluded from PPPI		Excluded from PPPS		Excluded from PPPI		Excluded from PPPS		Excluded from PPPI*		Excluded from PPPS*	
(b) (6)	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
	N	N	Y	Y	N	N	N	N	N	N	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	N	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y
	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
	N	N	Y	Y	N	N	N	N	N	N	Y	Y
	N	N	Y	Y	Y	Y	N	N	N	N	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y
	N	N	N	N	Y	Y	Y	Y	N	N	N	N
	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y
	N	N	N	Y	N	N	N	N	N	N	N	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	N	N	N	N	N	N	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	N	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	N	N	N	Y	N	N	N	N	N	N	N	Y
	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Reviewer's Comments:

1. The datasets used for this statistical review were from the original submission and the December 9, 2016 submission. The datasets contained numerous inconsistencies as detailed in this section. The reviewer tried to verify the data from the case report forms

when inconsistent information between datasets was observed. However, these could not be resolved in many cases.

2. Subjects (b) (6) withdrew from the study during the induction phase. In the dataset submitted on December 9, 2016, these subjects were correctly excluded from the PPPI but included in the PPPS without any explanation.

3. Subject (b) (6) completed the induction phase but was discontinued from the study by the investigator before the challenge phase. However, both patch types were included in the PPPS by the applicant in the dataset submitted on December 9, 2016.

4. For Subject (b) (6), the irritation assessments on Day (b) (6) and Da (b) (6) were done 9 and 8 minutes, respectively, after patch removal. The case report form contains comments that these are out-of-window irritation assessments according to the protocol. According to the protocol (Section 4), skin irritation assessments were to occur within 15-30 minutes following removal of each patch during induction phase. Therefore, the comments about out-of-window irritation assessments during the induction phase in the CRF are not consistent with the protocol.

5. The applicant did not submit the case report forms for Subject (b) (6) Also the submitted case report forms contained many errors such as placing the irritation assessment date and score for one patch at a place designated for another patch. For example, the irritation assessment for the first set of patches was not done for Subject (b) (6) but the assessment date and scores were not left blank for that patch and the irritation assessment information for the second set of patches was placed at that place instead. Additionally, the case report forms had too many data clarification forms attached which not only shows the data collection and recording problems in the first place, it also makes the data prone to inaccuracy. This resulted in additional pages of protocol deviations where new protocol deviations are identified along with the already reported ones. The arrangement of these pages is not clearly explained by the applicant.

3.2.8.2 Additional Exclusions by the FDA Reviewer

In addition to the patches discussed in Section 3.2.8.1, there were many patches that should be excluded from the PPPS or from both PPPI and PPPS but were not excluded by the applicant.

3.2.8.2.1 No Ninth Irritation Assessment in the Induction Phase

Subjects (b) (6) received all patches and had irritation scores for first 8 patches of both test and reference. The irritation assessments for the ninth patch in the induction phase were not performed for those subjects. The applicant included those patches in the PPPI and used LOCF to impute the missing irritation scores. However, according to FDA draft guidance, any patch with missing irritation assessments other than those missing because of discontinued patches due to excessive irritation should be excluded from the PPPI. The irritation scores for only the

patches discontinued due to excessive irritation should be included in the PPPI using the last observation carried forward (LOCF) method. Therefore, the patches from Subject (b) (6) have been excluded from FDA's PPPI. Since not all irritation assessments during the induction phase for these patches were made, these patches were also excluded from FDA's PPPS.

3.2.8.2.2 Exclusion Recommended in the OSIS Inspection Report

The Office of Study Integrity and Surveillance (OSIS) inspection report identified 12 subjects (b) (6) having an adhesion score of 4 (detached) and having a make-up patch.

The OSIS inspection report also states that except Subject (b) (6), in other 10 subjects the inspection verified that the replacement patch was detached for less than 24 hours, thus maintaining irritation and sensitization assessment eligibility but Subject (b) (6) were unaware of when the patch became fully detached, and thus, there was no assurance of whether the patch had been off for over 24 hours.

Of the 12 subjects affected by the protocol deviation, only two (Subject (b) (6)) had a cumulative irritancy index greater than 0. The decision to give these subjects make-up patches despite having fully detached patches altered the total number of skin irritation assessments from eight to nine. Thus, subjects (b) (6) would not have had the appropriate number of irritation assessments to be included in the per protocol analysis.

OSIS report recommended excluding data from the subject (b) (6) for per protocol analysis. The patches from these subjects were excluded from all per protocol populations in FDA's review.

Reviewer's Comment:

1. The OSIS inspection report identified 12 subjects having an adhesion score of 4 (detached) and having a make-up patch. However, Table 14 identifies many more subjects with make-up patches that were intended to replace the irritation scores of detached patches.

2. The OSIS inspection report states that except Subjects (b) (6), in other subjects who had a make-up patch for a detached patch, the inspection verified that the replacement patch had been detached for less than 24 hours. However, based on the data submitted on December 9, 2016, the reviewer could not confirm this. All patch detachment times were reported in the dataset as observed times as opposed to the actual times of detachment. In addition, the OSIS report is a direct contradiction to the ECD response submitted by the applicant on October 21, 2016. In response to Question 2 of the ECD letter, the applicant provided the following list of subjects who had detached patches for which date and time of detachment were unknown:

(b) (6)

This list includes all 10 subjects (b) (6)) for which the OSIS report claimed to have verified that the patch was detached for less than 24 hours. Since for none of those subjects the time difference between the application time of the patch that detached and the application time of the next patch or a replacement patch is less than 24 hours, the OSIS report's verification claim is inaccurate unless the applicant submitted wrong information in the ECD response and wrong datasets.

3. The OSIS inspection report identified only two subject (b) (6) who would not have had nine irritation assessments if the make-up patches were not used. However, this review identified many more such subjects. Please refer to Table 9 for detached patches and Table 14 for make-up patches. It appears from the OSIS report that one of the reasons for excluding these subjects from the per protocol analysis is that these subjects have cumulative irritancy index (mean irritation score) greater than zero. The information about whether the cumulative irritancy index is greater than zero is irrelevant in this case. All subjects by this protocol deviation would be affected and affect the results in the same way no matter what the cumulative irritancy index is.

3.2.8.2.3 Skipped Visits

As described in Section 3.2.2, the study design did not follow the Draft Guidance on Lidocaine and allowed subjects to skip a visit and keep the patches on until the next visit when they were evaluated for skin irritation. It resulted in having the same patch on for 4 or 5 days before an irritation assessment while the patches without a skipped visit were on for 2 or 3 days before the irritation assessment.

Table 8 gives the list of subjects who had at least 9 patch applications during the induction phase but had a skipped visit based on the difference between the patch application and irritation assessment dates. When these subjects skipped a visit, they were allowed to keep the patch on and come for the next scheduled assessment according to the protocol. Among the subjects in Table 8, Subjects (b) (6) had both patch types excluded from the applicant's PPPI and PPPS in both the original application and the dataset submitted on December 9, 2016 and from FDA's PPPI and PPPS. Also both patch types for Subjec (b) (6) were excluded by the FDA reviewer from the PPPI and PPPS because the subject did not have irritation assessment for the ninth patch. The rest of the subjects with a skipped visit were excluded from PPPI2, PPPI4, PPPI6, PPPS2, PPPS4 and PPPS6.

Table 8: Subjects with Skipped Visits During the Induction Phase

Patch Number for the Skipped Visit	Subject IDs
2	(b) (6)
3	
4	
5	
6	
7	
8	
9	

Source: Reviewer's analysis

3.2.8.2.4 Detached Patches and Make-up Patches

Many subjects had detached patches in this study. Table 9 shows the list of detached patches in the induction phase based on the submission of 9 December 2016. Among the patches in Table 9, both test and reference patches of Subjects (b) (6) were excluded from the applicant's PPPI in the original submission.

Table 9: Detached Patches in the Induction Phase Based on the 9 December 2016 Submission

Subject ID	Detached Test Patches	Detached Reference Patches
(b) (6)	5	5
	2	2
	2, 3	2, 3
	2	2, 3
	3	3
	1, 8	1, 8
	2	2
	4	4
	1, 3, 6, 7	1, 3, 6, 7
	3	3
	1	1
	2	2
		3
	2	2
	1	1
	1, 4	1, 4
	2	2
	3	3

(b) (6)	3, 6, 9	3, 6, 9
	8	8
	4	4
	3	3
	1	1
	3	3
	5	5
	3	3
	3	3
	3	3
	3	3
	3	3
	3	3
	3	3
	4	4
	2	2
	3	3
	7	7
	1	1
	2	2
	2	2
	3	3
	3, 4	3, 4
	1	1
	3	3

Table 10 lists the detached patches and the replaced patches in the challenge phase based on December 9, 2016 submission. Both detached patches of Subject (b) (6) were replaced. The replacement time was 12.5 hours after the original challenge phase patch application for both patches.

Table 10: Detached Patches in the Challenge Phase Based on the 9 December 2016 Submission

Subject ID	Detached Patches	Replaced Patches
(b) (6)	Test, Reference	
	Test, Reference	Test, Reference
	Reference	
	Test	
	Test	

Source: Reviewer's analysis

Among many inconsistencies in the submission, one is the mismatch between the patch detachment flag and the adhesion score for the corresponding patch in the dataset submitted on December 9, 2016. Table 11 lists the patches for which the patch detachment flag and the adhesion score do not match.

Table 11: Mismatch in Patch Detachment Flag and Adhesion Score in the 9 December 2016 Submission

		First Mismatch			Second Mismatch		
Subject ID	**Patch Type**	**Patch Number**	**Detached flag**	**Adhesion score**	**Patch Number**	**Detached flag**	**Adhesion score**
(b) (6)	T	2	Y	1			
	R	2	Y	1			
	T	3	Y	2			
	T	3	Y	2			
	R	1	Y	3	8	Y	3
	T	2	Y	1			
	T	4	Y	0			
	R	7	Y	3			
	R	2	Y	3			
	T	2	Y	2			
	R	4	Y	0			
	T	2	Y	3			
	T	4	Y	1			
	R	4	Y	3			
	R	3	Y	3			
	T	3	Y	2			
	T	3	Y	0			
	R	3	Y	0			
	T	3	Y	0			
	R	3	Y	1			
	R	4	Y	0			
	R	7	Y	0			
	T	1	Y	0			
	R	3	Y	3	4	Y	0
	R	3	Y	0			

Source: Reviewer's analysis

In an ECD dated October 3, FDA asked the applicant to provide data indicating if each patch detachment time listed was the actual detachment time or if that is the time when it was observed that patch had already detached. The applicant's December 9, 2016 submission contained these data. Since the patch detachment times for all patches were the times when patch detachment was first observed, and not known to be the actual times, the patch detachment times are right

censored. It is not possible to verify if the patch-free time is less than 24 hours except for the cases where the replacement patch was applied within 24 hours after the original patch application. Table 12 shows the number of detached patches and the number of replaced patches by patch number based on the data submitted on December 9, 2016. Table 13 lists the replaced patches. None of the replacement patches detached. Among the subjects in Table 13, both patches for Subjects (b) (6) had replacement patch applications within 24 hours after the original patch application. No other subject had a replacement patch application within 24 hours after the original patch application. Also, no subject had two consecutive regular patch applications within 24 hours. Therefore, the reviewer excluded all subject-patch type combinations from the PP populations (PPPI3-PPPI6 and PPPS3-PPPS6) whenever there was a detached patch except for the patches for Subjects (b) (6)

Table 12: Frequencies of Detached and Replaced Patches in the Induction Phase by Patch Number and in the Challenge Phase

Patch Number	Patch Detachment			Number of Patches Replaced
	Missing	No	Yes	
1	0	480	16	2
2	8	468	20	0
3	16	440	40	11
4	20	466	10	2
5	22	470	4	2
6	26	466	4	0
7	28	464	4	0
8	30	462	4	0
9	30	464	2	0
Makeup	424	72	0	0
Challenge Phase	34	455	7	2

Source: Reviewer's analysis

Table 13: List of Replacement Patches

Subject ID	Patch Type	Patch Number	Original Patch Application Date and Time	Original Patch Detachment Date and Time (Observed)	Replacement Patch Application Date and Time	Diff*
(b) (6)	R	5	(b) (6)			32:23
	T	5				32:23
	R	Ch**				12:30
	T	Ch**				12:30
	R	3				47:57
	T	3				47:57
	R	3				49:46

(b) (6)			(b) (6)	
	T	3		49:46
	R	3		51:47
	R	3		51:06
	T	3		51:06
	R	4		07:47
	T	4		07:47
	R	3		55:55
	T	3		55:55
	R	1		24:36
	T	1		24:36
	R	3		54:05
	T	3		54:05

* Diff = Difference between original and replacement patch application times in hours and minutes.
Patch Type: T=Test, R=Reference
** Ch=Challenge phase patch
Green font indicates that the replacement patch was applied with 24 hours of the original patch application.
Source: Reviewer's analysis

Make-up patches were used at the end of the induction phase on the subjects who had detached (an adhesion score of 4) or partially detached (an adhesion score of 3) patches. Table 14 shows the list of make-up patches and identifies the corresponding patches with adhesion score 3 and 4 whose irritation scores the applicant intended to replace by the irritation score of the make-up patches. When there are multiple patches that the same make-up patch was intended to replace, the number of patches is essentially reduced because the irritation score of a single make-up patch replaces that of multiple patches as described in the reviewer's comment in Section 3.2.2. For that reason this review ignored all make-up patches.

Table 14: List of Make-up Patches

Subject ID	Patch Type	Patch number with adhesion score 3	Patch number with adhesion score 4
(b) (6)	Reference	2, 6	5
	Test	6	5
	Test	4	
	Reference		2
	Reference		3
	Test		2
	Test	5	
	Reference	2	
	Test	2	
	Reference	2	
	Reference	5	
	Test	5	
	Reference	9	3

(b) (6)

Test	9	
Reference	2	
Test	1	
Reference	1, 7, 8	
Test	7	1, 8
Reference		2
Reference	2	
Test	2	
Reference	7	1, 3, 6
Test	2, 4, 5	1, 3, 6, 7
Reference	2	
Reference	4	
Reference	1, 4	
Test	2	
Reference	1	
Test	1	
Reference	2	3
Test	1	
Reference	2	
Test		2
Reference	6	
Reference		2
Reference	2	
Reference		1
Test		1, 4
Reference	1, 9	
Test	8, 9	
Test	7	
Reference	1, 2	3, 6, 9
Test	2	3, 6, 9
Reference	1, 2, 4	
Reference	2, 5	
Test	4	
Test	3	
Test	1	
Test	1	
Reference		3
Test		3
Reference	3	
Test		3
Reference	5	
Reference		3
Reference		3

(b) (6)			
	Test		3
	Reference		3
	Test	3	
	Test	3	
	Test	8	3
	Test	3	4
	Reference	6	3
	Test	6	3
	Test		7
	Reference	5	
	Reference	2, 3	
	Reference		1
	Test	8	
	Test	8	
	Reference		1
	Test	3, 8	1

Source: Reviewer's analysis

Reviewer's Comments:

According to the original submission the test patch of Subjec (b) (6) and the reference patches of Subjects (b) (6) detached during the challenge phase. However, as shown in Table 10, based on the December 9, 2016 submission, the test patches of Subjects (b) (6) and the reference patch of Subjec (b) (6) detached during the challenge phase. These conflicting data give an indication of a possibility of reversing the test and reference data for some or all subjects in the dataset. If that happened, all analyses would be wrong. This gives a strong reason why inconsistent data should never be considered for an approval.

3.2.8.3 FDA's Analysis Populations

Due to the non-standard design and potential problems with skipped visits and detached patches as discussed in Sections 3.2.8.2.3 and 3.2.8.2.4, the reviewer considered several per protocol populations for irritation and per protocol populations for sensitization. The populations are named as PPPI1, PPPI2, etc. for irritation and PPPS1, PPPS2, etc. for sensitization. Following are the definitions of the populations and the lists of patches excluded from the populations.

3.2.8.3.1 PPPI1 and PPPS1

The patches excluded from PPPI1 are:

- A patch type that did not have all nine patch applications or did not have all nine irritation assessments for a subject. This set consists of all patches that are excluded from

FDA's PPPI in Table 7 and all patches from Subjects (b) (6). Please refer to Sections 3.2.8.1 and 3.2.8.2.1 for more details.

- All patches from Subjects (b) (6). This is based on the OSIS inspection report. Please refer to Section 3.2.8.2.2 for more details.

The patches excluded from PPPS1 are:

- A patch type that did not have all nine irritation assessments for a subject or did not have challenge phase patch application or the challenge phase patch was removed before 44 hours or the challenge phase patch detached and the detachment time was unknown or the challenge phase irritation assessments were not done. This set consists of all patches that are excluded from FDA's PPPS in Table 7 and all patches from Subjects (b) (6) Please refer to Sections 3.2.8.1 and 3.2.8.2.1 for more details.
- All patches from Subjects (b) (6). This is based on the OSIS inspection report. Please refer to Section 3.2.8.2.2 for more details.

The lists of patches excluded from PPPI1 and PPPS1 are presented in Table 15.

Table 15: Patches Excluded from PPPI1 and PPPS1

Subject ID	Exlcuded from PPPI1		Excluded from PPPS1	
(b) (6)	Test	Reference	Test	Reference
			Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
				Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y

(b) (6)				
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
				Y
	Y	Y	Y	Y
	Y	Y	Y	Y

Source: Reviewer's analysis

3.2.8.3.2 PPPI2 and PPPS2

The patches excluded from PPPI2 are:

- All patches excluded from PPPI1.
- All patches from the subjects who skipped a visit during the induction phase. Please refer to Section 3.2.8.2.3 for more details.

The patches excluded from PPPS2 are:

- All patches excluded from PPPS1.
- All patches from the subjects who skipped a visit during the induction phase. Please refer to Section 3.2.8.2.3 for more details.

All patches for the following subjects in addition to the patches listed in Table 15 were excluded from PPPI2 and PPPS2:

(b) (6)

3.2.8.3.3 PPPI3 and PPPS3

The patches excluded from PPPI3 are:

- All patches excluded from PPPI1.
- All patches that were detached during the induction phase based on the patch detachment flag but not known to be replaced within 24 hours after detachment. The datasets submitted on December 9, 2016 were used for this determination. Please refer to Section 3.2.8.2.4 for more details.

The patches excluded from PPPS3 are:

- All patches excluded from PPPS1.
- All patches that were detached during the induction or challenge phase based on the patch detachment flag but not known to be replaced within 24 hours after detachment. The datasets submitted on December 9, 2016 were used for this determination. Please refer to Section 3.2.8.2.4 for more details.

The lists of patches excluded from PPPI3 and PPPS3 are presented in Table 16.

Table 16: Patches Excluded from PPPI3 and PPPS3

Subject ID	Exlcuded from PPPI3		Excluded from PPPS3	
	Test	Reference	Test	Reference
(b) (6)	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
		Y		Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y

(b) (6) [redacted]	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y

Source: Reviewer's analysis

3.2.8.3.4 PPPI4 and PPPS4

The patches excluded from PPPI4 are:

- All patches excluded from PPPI3.
- All patches from the subjects who skipped a visit during the induction phase. Please refer to Section 3.2.8.2.3 for more details.

The patches excluded from PPPS4:

- All patches excluded from PPPS3.
- All patches from the subjects who skipped a visit during the induction phase. Please refer to Section 3.2.8.2.3 for more details.

All patches for the following subjects in addition to the patches listed in Table 16 were excluded from PPPI4 and PPPS4:

(b) (6)

3.2.8.3.5 PPPI5 and PPPS5

The patches excluded from PPPI5 are:

- All patches excluded from PPPI1.
- All patches that were detached during the induction phase based on the adhesion scores but not known to be replaced within 24 hours after detachment. The datasets submitted on December 9, 2016 were used for this determination. Please refer to Section 3.2.8.2.4 for more details.

The patches excluded from PPPS5 are:

- All patches excluded from PPPS1.
- All patches that were detached during the induction or challenge phase based on the adhesion scores but not known to be replaced within 24 hours after detachment. The datasets submitted on December 9, 2016 were used for this determination. Please refer to Section 3.2.8.2.4 for more details.

The lists of patches excluded from PPPI5 and PPPS5 are presented in Table 17.

Table 17: Patches Excluded from PPPI5 and PPPS5

Subject ID	Exlcuded from PPPI5		Excluded from PPPS5	
(b) (6)	Test	Reference	Test	Reference
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
		Y		Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
		Y	Y	Y
	Y	Y	Y	Y

(b) (6)

		Y	Y
Y		Y	
	Y		Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y		Y	
	Y		Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
		Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
		Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y		Y	
	Y		Y
	Y		Y
Y	Y	Y	Y
Y	Y	Y	Y
	Y		Y
Y		Y	
Y	Y	Y	Y
Y		Y	
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y

(b) (6)				
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y		Y	
	Y	Y	Y	Y
			Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y	Y	Y	Y
	Y		Y	

Source: Reviewer's analysis

3.2.8.3.6 PPPI6 and PPPS6

The patches excluded from PPPI6 are:

- All patches excluded from PPPI5.
- All patches from the subjects who skipped a visit during the induction phase. Please refer to Section 3.2.8.2.3 for more details.

The patches excluded from PPPS6 are:

- All patches excluded from PPPS5.
- All patches from the subjects who skipped a visit during the induction phase. Please refer to Section 3.2.8.2.3 for more details.

The following patches in addition to the patches listed in Table 17 were excluded from PPPI6 and PPPS6:

- Both patches for Subjects: (b) (6)
- Reference patch for Subjects (b) (6)

3.2.9 Demographic and Baseline Characteristics

A summary of demographic and baseline characteristics (gender, race and age) for all enrolled subjects, which was same as the safety population in this study, is presented in Table 18. Approximately 74% subjects were female. Majority of the subjects were black (approximately 54%) followed by white (approximately 44%). The age range was 18 to 69 years. The average and median ages were 41.4 and 43 years, respectively. The study was conducted at a single site (b) (4) in USA.

Table 18: Demographic and Baseline Characteristics for Irritation and Sensitization Study: Gender, Race and Age

		All Enrolled (N=248)
Gender	Female	184 (74.19%)
	Male	64 (25.81%)
Race	Asian	3 (1.21%)
	Black	135 (54.44%)
	White	110 (44.35%)
Age Group in Years	18-40	111 (44.76%)
	41-64	129 (52.02%)
	65-75	8 (3.23%)
Age in Years	Mean, SD	41.39, 12.22
	Min, Max	18, 69
	Q1, Median, Q3	33, 43, 49

Source: Reviewer's analysis

3.2.10 Results and Conclusions

3.2.10.1 Applicant's Analysis Results

The irritation score (on a scale of 0 to 13) for each patch at each evaluation was the sum of the dermal response score (on a scale of 0 to 7) and the score for other effects (on a scale of 0 to 6) as given in Table 2 and Table 3. The cumulative irritancy index (CII) was defined as the sum of all irritation scores across readings during the induction/challenge phase divided by the number of readings (9 readings). The cumulative dermal response index and the cumulative other effects index were defined similarly.

A summary of the cumulative irritancy index, cumulative dermal response index and cumulative other effects index by treatment and by treatment and cohort for the full irritation analysis population in the induction phase is presented in Table 19 and that in the challenge phase is presented in Table 20.

Table 19: Summary of Cumulative Irritancy Index in Induction Phase by Treatment and Cohort in Full Irritation Analysis Population per Applicant

Parameter	Statistic	Overall		Cohort 1		Cohort 2	
		Test	Reference	Test	Reference	Test	Reference
Cumulative Irritancy Index	N	228	228	112	112	116	116
	Mean (SD)	0.211 (0.3535)	0.212 (0.3442)	0.170 (0.3009)	0.170 (0.3047)	0.250 (0.3624)	0.253 (0.3757)
	Median	0	0	0	0	0	0

	Min, Max	0, 1.44	0, 1.67	0, 1.22	0, 1.11	0, 1.44	0, 1.67
Cumulative Dermal Response Index	N	228	228	112	112	116	116
	Mean (SD)	0.211 (0.3535)	0.212 (0.3442)	0.170 (0.3009)	0.170 (0.3047)	0.250 (0.3624)	0.253 (0.3757)
	Median	0	0	0	0	0	0
	Min, Max	0, 1.44	0,1.67	0, 1.22	0, 1.11	0, 1.44	0, 1.67
Cumulative Other Effects Index	N	228	228	112	112	116	116
	Mean (SD)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Median	0	0	0	0	0	0
	Min, Max	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0

Source: Clinical Study Report, Study RP-LID-SSI, Table 14.4.3.1 and Table 14.4.3.2

Table 20: Summary of Cumulative Irritancy Index in Challenge Phase by Treatment and Cohort in Full Irritation Analysis Population per Applicant

Parameter	Statistic	Overall		Cohort 1		Cohort 2	
		Test	Reference	Test	Reference	Test	Reference
Cumulative Irritancy Index	N	225	225	110	110	115	115
	Mean (SD)	0.061 (0.1667)	0.050 (0.1475)	0.059 (0.1821)	0.048 (0.1641)	0.063 (0.1512)	0.052 (0.1303)
	Median	0	0	0	0	0	0
	Min, Max	0, 1.50	0, 1.50	0, 1.50	0, 1.50	0, 0.75	0, 0.50
Cumulative Dermal Response Index	N	225	225	110	110	115	115
	Mean (SD)	0.061 (0.1667)	0.050 (0.1475)	0.059 (0.1821)	0.048 (0.1641)	0.063 (0.1512)	0.052 (0.1303)
	Median	0	0	0	0	0	0
	Min, Max	0, 1.50	0, 1.50	0, 1.50	0, 1.50	0, 0.75	0, 0.50
Cumulative Other Effects Index	N	225	225	110	110	115	115
	Mean (SD)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Median	0	0	0	0	0	0
	Min, Max	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0

Source: Clinical Study Report, Study RP-LID-SSI, Table 14.4.5.1 and Table 14.4.5.2

The individual CIIs, the individual irritancy index, the individual cumulative dermal response index and the individual cumulative other effects index generated during the induction phase were tested for product differences using the 2-way analysis of variance (ANOVA) including main effects of subject and product, without interaction using the PROC GLM. For the test product to be no more irritating than the RLD, the upper bound of the one-sided 95% confidence interval of the difference between the products had to be no greater than 0.11 based on the protocol. The upper bound of the 95% one-sided confidence interval of the difference between the two products was calculated to be 0.015 for both the individual irritancy and dermal response

indices. No variance for other effect index was observed; all values were zero. These results are summarized in Table 21.

Table 21: Analysis of Cumulative Irritancy Index in the Induction Phase in the Full Irritation Analysis Population per Applicant

Parameter	Least Square Means		Mean of Test - Reference	One-Sided 95% Upper Confidence Bound for Test - Reference
	Test	Reference		
Cumulative Irritancy Index	0.211	0.212	-0.001	0.015
Cumulative Dermal Response Index	0.211	0.212	-0.001	0.015
Cumulative Other Effects Index	0	0	0	0

Source: Clinical Study Report, Study RP-LID-SSI, Table 14.4.4

There was no observation of a maximum irritation score of 13, a maximum dermal response score of 7 or a maximum other effects score of 6 reported for any patch. No patch was removed due to an unacceptable degree of irritation.

The applicant concluded that taken together, these data demonstrated that there was no difference for skin irritancy between the test and the reference patches.

In addition to the protocol specified analysis, the applicant conducted a post-hoc analysis as per "FDA's Draft Guidance on Nicotine Extended Release Transdermal Patch" with regard to the skin irritation and sensitization assessment. This post-hoc analysis was performed using the 2-way analysis of variance (ANOVA) including main effects of subject and product, without interaction using the PROC GLM. The results of cumulative irritancy scores demonstrated non-inferiority as the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score was less than 0. The results are presented in Table 22 and are consistent with the pre-specified statistical analysis results.

Table 22: Post-Hoc Analysis of Cumulative Irritancy Index in the Induction Phase in the Full Irritation Analysis Population per Applicant

Parameter	Least Square Means		Mean of Test - Reference	One-Sided 95% Upper Confidence Bound for Test - Reference
	Test	Reference		
Cumulative Irritancy Index	0.211	0.212	-0.052	-0.034
Cumulative Dermal Response Index	0.211	0.212	-0.052	-0.034
Cumulative Other Effects Index	0	0	0	0

Source: Clinical Study Report, Study RP-LID-SSI, Table 10

Sensitization of test versus reference study products was based on irritation scores obtained during the challenge phase and whether the reactions were indicative of a sensitization reaction by the investigator. The full sensitization analysis population consisted of 227 (91.5%) subjects. There were 111 (90.2%) and 116 (92.8%) subjects in Cohorts 1 and 2, respectively, of both the test sensitization analysis population and reference sensitization analysis population. There was no evidence of skin sensitization reaction following removal of either the test or reference challenge patch. The results are shown in Table 23. No patch was removed due to strong skin sensitization.

Table 23: Summary of the Number of Skin Sensitization Reactions in Full Sensitization Analysis Population per Applicant

Parameter	Scheduled Time Point after Patch Removal	Treatment	
		Test (N=227)	Reference (N=227)
Number of Skin Sensitization Reactions	30 min	0	0
	24 hrs	0	0
	48 hrs	0	0
	72 hrs	0	0

Source: Clinical Study Report, Study RP-LID-SSI, Table 11

Reviewer's Comments:

1. The applicant did not use any letter score for the other effects. The applicant's other effects numeric scale was different from FDA's other effects numeric scale. This difference is shown in Table 4.

2. According to the Draft Guidance on Lidocaine, the applicant should provide a frequency table showing the number of applications of each test article with each combined dermal response and other effects score using the last observation carried forward (LOCF) for subjects who discontinued a test article because of unacceptable irritation. The applicant did not provide any such table.

3. The Draft Guidance on Lidocaine states the following: "To demonstrate non-inferiority of the test product compared to the RLD with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score must be less than or equal to 0." However, the applicant's criterion for non-inferiority in the primary analysis was different. The applicant considered the test product to be non-inferior to the reference product if the upper bound of the one-sided 95% confidence interval of the difference between the products (test - reference) was not greater than 0.11. The applicant did not provide any justification in the protocol, statistical analysis plan or clinical study report for its criterion for non-inferiority in the primary analysis and how they determined the non-inferiority margin of 0.11.

3.2.10.2 Reviewer's Analysis Results

Analyses of irritation in PPPI1 to PPPI6 are provided in Sections 3.2.10.2.1 to 3.2.10.2.6, respectively and analyses of sensitization in PPPS1 to PPPPS6 are provided in Section 3.2.10.2.7. No patches were discontinued or moved due to excessive irritation.

3.2.10.2.1 Irritation Analysis Results in PPPI1

Table 24 shows the number and percent of applications by induction phase patch number and patch type with a specific combined "dermal response" and "other effects" score in PPPI1. A summary of mean irritation scores during the induction phase in PPPI1 is presented in Table 25.

Table 24: Number (%) of Applications by Induction Phase Patch Number and Patch Type with a Specific Combined "Dermal Response" and "Other Effect" Score in the PPPI1

Patch No: Treatment	Combined "Dermal Response" and "Other Effect" Score Frequency, %							
	0N		1N		2N		3N	
1:Test	193	86.94%	27	12.16%	2	0.90%	0	0.00%
1:Reference	194	87.39%	26	11.71%	2	0.90%	0	0.00%
2:Test	189	85.14%	30	13.51%	3	1.35%	0	0.00%
2:Reference	189	85.14%	31	13.96%	2	0.90%	0	0.00%
3:Test	173	77.93%	42	18.92%	7	3.15%	0	0.00%
3:Reference	175	78.83%	40	18.02%	6	2.70%	1	0.45%
4:Test	174	78.38%	45	20.27%	3	1.35%	0	0.00%
4:Reference	173	77.93%	46	20.72%	3	1.35%	0	0.00%
5:Test	178	80.18%	41	18.47%	3	1.35%	0	0.00%
5:Reference	174	78.38%	45	20.27%	3	1.35%	0	0.00%
6:Test	173	77.93%	48	21.62%	1	0.45%	0	0.00%
6:Reference	177	79.73%	42	18.92%	3	1.35%	0	0.00%
7:Test	170	76.58%	51	22.97%	1	0.45%	0	0.00%
7:Reference	167	75.23%	52	23.42%	3	1.35%	0	0.00%
8:Test	181	81.53%	41	18.47%	0	0.00%	0	0.00%
8:Reference	181	81.53%	40	18.02%	1	0.45%	0	0.00%
9:Test	176	79.28%	45	20.27%	1	0.45%	0	0.00%

9:Reference	177	79.73%	41	18.47%	4	1.80%	0	0.00%

Please refer to Section 3.2.3 for the conversion from letter score to numerical score.
Source: Reviewer's analysis.

Table 25: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI1 per FDA Reviewer

Product	N	Mean (SD)	Min	First Quartile	Median	Third Quartile	Max
A (Test)	222	0.206 (0.323)	0	0	0	0.333	1.444
B (Reference)	222	0.210 (0.345)	0	0	0	0.333	1.667

Source: Reviewer's analysis

The non-inferiority analysis of test patch against the reference patch based on the mean irritation score in PPPI1 using a linear model is shown in Table 26. In the model, the mean irritation score was the response and treatment and subject were fixed effects. The one-sided 95% upper confidence bound was -0.0379 which being negative showed that the test is non-inferior to the reference.

Table 26: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI1 per FDA

Variable	Hypotheses	LSmean Test	LSmean Reference	Estimate of $\mu_A - 1.25*\mu_B$	One-Sided 95% Upper Confidence Bound
Mean Irritation Score	H_0: $\mu_A - 1.25*\mu_B \geq 0$ H_1: $\mu_A - 1.25*\mu_B < 0$	0.2062	0.2102	-0.0566	-0.0379

Source: Reviewer's analysis

The proportion of subjects in PPPI1 with and without a meaningful degree of irritation (at least one irritation score ≥ 3) is cross-tabulated for the test versus reference products in Table 27. A test for non-inferiority of the test patch to the reference patch in terms of proportion of patches with a meaningful degree of irritation in PPPI1 is presented in Table 28. There was no test patch and 1 (00.45%) reference patch with at least one irritation score ≥ 3. The point estimate of $P_T - P_R$, the difference between proportion of test and reference patches with a meaningful degree of irritation is -0.0045 (-0.45%) and the one-sided 95% upper bound for $P_T - P_R$ is 0.01204.

Table 27: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI1

		Test Product		
		Max Irritation Score < 3	Max Irritation Score ≥ 3	Total
Reference Product	Max Irritation Score < 3	221	0	221
	Max Irritation Score ≥ 3	1	0	1
	Total	222	0	222

Source: Reviewer's analysis

Table 28: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful Degree of Irritation During the Induction Phase in PPPI1

Hypothesis	Proportion of Test Score ≥ 3 (P_T) (N=222)	Proportion of Reference Score ≥ 3 (P_R) (N=222)	Point Estimate of $P_T - P_R$	One-sided 95% Upper Confidence Limit of $P_T - P_R$
H_0: $P_T - P_R > \delta$ (inferior) H_1: $P_T - P_R \leq \delta$ (non-inferior)	0.0000	0.0045	-0.0045	0.01204

Source: Reviewer's analysis

3.2.10.2.2 Irritation Analysis Results in PPPI2

Table 29 shows the number and percent of applications by induction phase patch number and patch type with a specific combined "dermal response" and "other effects" score in PPPI2. A summary of mean irritation scores during the induction phase in PPPI2 is presented in Table 30.

Table 29: Number (%) of Applications by Induction Phase Patch Number and Patch Type with a Specific Combined "Dermal Response" and "Other Effect" Score in the PPPI2

Patch No: Treatment	Combined "Dermal Response" and "Other Effect" Score Frequency, %							
	0N		1N		2N		3N	
1:Test	170	86.73%	24	12.24%	2	1.02%	0	0.00%
1:Reference	171	87.24%	24	12.24%	1	0.51%	0	0.00%
2:Test	167	85.20%	26	13.27%	3	1.53%	0	0.00%
2:Reference	165	84.18%	29	14.80%	2	1.02%	0	0.00%
3:Test	152	77.55%	37	18.88%	7	3.57%	0	0.00%
3:Reference	153	78.06%	36	18.37%	6	3.06%	1	0.51%

4:Test	155	79.08%	38	19.39%	3	1.53%	0	0.00%
4:Reference	153	78.06%	40	20.41%	3	1.53%	0	0.00%
5:Test	157	80.10%	36	18.37%	3	1.53%	0	0.00%
5:Reference	157	80.10%	36	18.37%	3	1.53%	0	0.00%
6:Test	151	77.04%	44	22.45%	1	0.51%	0	0.00%
6:Reference	155	79.08%	38	19.39%	3	1.53%	0	0.00%
7:Test	149	76.02%	46	23.47%	1	0.51%	0	0.00%
7:Reference	146	74.49%	47	23.98%	3	1.53%	0	0.00%
8:Test	159	81.12%	37	18.88%	0	0.00%	0	0.00%
8:Reference	159	81.12%	36	18.37%	1	0.51%	0	0.00%
9:Test	156	79.59%	39	19.90%	1	0.51%	0	0.00%
9:Reference	156	79.59%	36	18.37%	4	2.04%	0	0.00%

Please refer to Section 3.2.3 for the conversion from letter score to numerical score.
Source: Reviewer's analysis.

Table 30: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI2 per FDA Reviewer

Product	N	Mean (SD)	Min	First Quartile	Median	Third Quartile	Max
A (Test)	196	0.209 (0.341)	0	0	0	0.333	1.444
B (Reference)	196	0.214 (0.354)	0	0	0	0.333	1.667

Source: Reviewer's analysis

The non-inferiority analysis of test patch against the reference patch based on the mean irritation score in PPPI2 using a linear model is shown in Table 31. In the model, the mean irritation score was the response and treatment and subject were fixed effects. The one-sided 95% upper confidence bound was -0.0381 which being negative showed that the test is non-inferior to the reference.

Table 31: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI2 per FDA

Variable	Hypotheses	LSmean Test	LSmean Reference	Estimate of $\mu_A - 1.25*\mu_B$	One-Sided 95% Upper

					Confidence Bound
Mean Irritation Score	H_0: $\mu_A - 1.25*\mu_B \geq 0$ H_1: $\mu_A - 1.25*\mu_B < 0$	0.2092	0.2137	-0.0580	-0.0381

Source: Reviewer's analysis

The proportion of subjects in PPPI2 with and without a meaningful degree of irritation (at least one irritation score ≥ 3) is cross-tabulated for the test versus reference products in Table 32. A test for non-inferiority of the test patch to the reference patch in terms of proportion of patches with a meaningful degree of irritation in PPPI2 is presented in Table 33. There was no test patch and 1 (00.51%) reference patch with at least one irritation score ≥ 3. The point estimate of $P_T - P_R$, the difference between proportion of test and reference patches with a meaningful degree of irritation is -0.0051 (-0.51%) and the one-sided 95% upper bound for $P_T - P_R$ is 0.01362.

Table 32: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI2

		Test Product		
		Max Irritation Score < 3	**Max Irritation Score ≥ 3**	**Total**
Reference Product	**Max Irritation Score < 3**	195	0	195
	Max Irritation Score ≥ 3	1	0	1
	Total	196	0	196

Source: Reviewer's analysis

Table 33: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful Degree of Irritation During the Induction Phase in PPPI2

Hypothesis	Proportion of Test Score ≥ 3 (P_T) (N=196)	Proportion of Reference Score ≥ 3 (P_R) (N=196)	Point Estimate of $P_T - P_R$	One-sided 95% Upper Confidence Limit of $P_T - P_R$
H_0: $P_T - P_R > \delta$ (inferior) **H_1: $P_T - P_R \leq \delta$ (non-inferior)**	0.0000	0.0051	-0.0051	0.01362

Source: Reviewer's analysis

3.2.10.2.3 Irritation Analysis Results in PPPI3

Table 34 shows the number and percent of applications by induction phase patch number and patch type with a specific combined "dermal response" and "other effects" score in PPPI3. A summary of mean irritation scores during the induction phase in PPPI3 is presented in Table 35.

Table 34: Number (%) of Applications by Induction Phase Patch Number and Patch Type with a Specific Combined "Dermal Response" and "Other Effect" Score in the PPPI3

Patch No: Treatment	Combined "Dermal Response" and "Other Effect" Score Frequency, %							
	0N		1N		2N		3N	
1:Test	167	86.53%	24	12.44%	2	1.04%	0	0.00%
1:Reference	165	85.94%	25	13.02%	2	1.04%	0	0.00%
2:Test	162	83.94%	29	15.03%	2	1.04%	0	0.00%
2:Reference	161	83.85%	30	15.63%	1	0.52%	0	0.00%
3:Test	147	76.17%	39	20.21%	7	3.63%	0	0.00%
3:Reference	150	78.13%	36	18.75%	5	2.60%	1	0.52%
4:Test	149	77.20%	42	21.76%	2	1.04%	0	0.00%
4:Reference	148	77.08%	41	21.35%	3	1.56%	0	0.00%
5:Test	152	78.76%	38	19.69%	3	1.55%	0	0.00%
5:Reference	147	76.56%	42	21.88%	3	1.56%	0	0.00%
6:Test	147	76.17%	45	23.32%	1	0.52%	0	0.00%
6:Reference	151	78.65%	38	19.79%	3	1.56%	0	0.00%
7:Test	145	75.13%	47	24.35%	1	0.52%	0	0.00%
7:Reference	141	73.44%	48	25.00%	3	1.56%	0	0.00%
8:Test	154	79.79%	39	20.21%	0	0.00%	0	0.00%
8:Reference	154	80.21%	37	19.27%	1	0.52%	0	0.00%
9:Test	150	77.72%	42	21.76%	1	0.52%	0	0.00%
9:Reference	151	78.65%	37	19.27%	4	2.08%	0	0.00%

Please refer to Section 3.2.3 for the conversion from letter score to numerical score.
Source: Reviewer's analysis.

Table 35: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI3 per FDA Reviewer

Product	N	Mean (SD)	Min	First Quartile	Median	Third Quartile	Max

A (Test)	193	0.220 (0.336)	0	0	0	0.333	1.444
B (Reference)	192	0.224 (0.350)	0	0	0	0.444	1.667

Source: Reviewer's analysis

The non-inferiority analysis of test patch against the reference patch based on the mean irritation score in PPPI3 using a linear model is shown in Table 36. In the model, the mean irritation score was the response and treatment and subject were fixed effects. The one-sided 95% upper confidence bound was -0.0394 which being negative showed that the test is non-inferior to the reference.

Table 36: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI3 per FDA

Variable	Hypotheses	LSmean Test	LSmean Reference	Estimate of $\mu_A - 1.25*\mu_B$	One-Sided 95% Upper Confidence Bound
Mean Irritation Score	H_0: $\mu_A - 1.25*\mu_B \geq 0$ H_1: $\mu_A - 1.25*\mu_B < 0$	0.2205	0.2245	-0.0602	-0.0394

Source: Reviewer's analysis

The proportion of subjects in PPPI3 with and without a meaningful degree of irritation (at least one irritation score ≥ 3) is cross-tabulated for the test versus reference products in Table 37. A test for non-inferiority of the test patch to the reference patch in terms of proportion of patches with a meaningful degree of irritation in PPPI3 is presented in Table 38. There was no test patch and 1 (00.52%) reference patch with at least one irritation score ≥ 3. The point estimate of $P_T - P_R$, the difference between proportion of test and reference patches with a meaningful degree of irritation is -0.0052 (-0.52%) and the one-sided 95% upper bound for $P_T - P_R$ is 0.01390.

Table 37: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI3

		Test Product		
		Max Irritation Score < 3	**Max Irritation Score ≥ 3**	**Total**
Reference Product	**Max Irritation Score < 3**	191	0	191
	Max Irritation Score ≥ 3	1	0	1
	Total	192	0	192

Source: Reviewer's analysis

Table 38: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful Degree of Irritation During the Induction Phase in PPPI3

Hypothesis	Proportion of Test Score ≥ 3 (P_T)	Proportion of Reference Score ≥ 3	Point Estimate of $P_T - P_R$	One-sided 95% Upper Confidence

	(N=192)	(P_R) (N=192)		Limit of P_T - P_R
H_0: P_T - P_R > δ (inferior) H_1: P_T - P_R ≤ δ (non-inferior)	0.0000	0.0052	-0.0052	0.01390

Source: Reviewer's analysis

3.2.10.2.4 Irritation Analysis Results in PPPI4

Table 39 shows the number and percent of applications by induction phase patch number and patch type with a specific combined "dermal response" and "other effects" score in PPPI4. A summary of mean irritation scores during the induction phase in PPPI4 is presented in Table 40.

Table 39: Number (%) of Applications by Induction Phase Patch Number and Patch Type with a Specific Combined "Dermal Response" and "Other Effect" Score in the PPPI4

Patch No: Treatment	Combined "Dermal Response" and "Other Effect" Score Frequency, %							
	0N		1N		2N		3N	
1:Test	152	86.36%	22	12.50%	2	1.14%	0	0.00%
1:Reference	151	86.29%	23	13.14%	1	0.57%	0	0.00%
2:Test	148	84.09%	26	14.77%	2	1.14%	0	0.00%
2:Reference	145	82.86%	29	16.57%	1	0.57%	0	0.00%
3:Test	133	75.57%	36	20.45%	7	3.98%	0	0.00%
3:Reference	135	77.14%	34	19.43%	5	2.86%	1	0.57%
4:Test	137	77.84%	37	21.02%	2	1.14%	0	0.00%
4:Reference	135	77.14%	37	21.14%	3	1.71%	0	0.00%
5:Test	139	78.98%	34	19.32%	3	1.70%	0	0.00%
5:Reference	137	78.29%	35	20.00%	3	1.71%	0	0.00%
6:Test	133	75.57%	42	23.86%	1	0.57%	0	0.00%
6:Reference	136	77.71%	36	20.57%	3	1.71%	0	0.00%
7:Test	131	74.43%	44	25.00%	1	0.57%	0	0.00%
7:Reference	127	72.57%	45	25.71%	3	1.71%	0	0.00%
8:Test	140	79.55%	36	20.45%	0	0.00%	0	0.00%
8:Reference	140	80.00%	34	19.43%	1	0.57%	0	0.00%
9:Test	137	77.84%	38	21.59%	1	0.57%	0	0.00%

9:Reference	137	78.29%	34	19.43%	4	2.29%	0	0.00%

Please refer to Section 3.2.3 for the conversion from letter score to numerical score.
Source: Reviewer's analysis.

Table 40: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI4 per FDA Reviewer

Product	N	Mean (SD)	Min	First Quartile	Median	Third Quartile	Max
A (Test)	176	0.223 (0.345)	0	0	0	0.333	1.444
B (Reference)	175	0.227 (0.360)	0	0	0	0.444	1.667

Source: Reviewer's analysis

The non-inferiority analysis of test patch against the reference patch based on the mean irritation score in PPPI4 using a linear model is shown in Table 41. In the model, the mean irritation score was the response and treatment and subject were fixed effects. The one-sided 95% upper confidence bound was -0.0407 which being negative showed that the test is non-inferior to the reference.

Table 41: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI4 per FDA

Variable	Hypotheses	LSmean Test	LSmean Reference	Estimate of $\mu_A - 1.25*\mu_B$	One-Sided 95% Upper Confidence Bound
Mean Irritation Score	H_0: $\mu_A - 1.25*\mu_B \geq 0$ H_1: $\mu_A - 1.25*\mu_B < 0$	0.2229	0.2279	-0.0621	-0.0407

Source: Reviewer's analysis

The proportion of subjects in PPPI4 with and without a meaningful degree of irritation (at least one irritation score ≥ 3) is cross-tabulated for the test versus reference products in Table 42. A test for non-inferiority of the test patch to the reference patch in terms of proportion of patches with a meaningful degree of irritation in PPPI4 is presented in Table 43. There was no test patch and 1 (00.57%) reference patch with at least one irritation score ≥ 3. The point estimate of $P_T - P_R$, the difference between proportion of test and reference patches with a meaningful degree of irritation is -0.0057 (-0.57%) and the one-sided 95% upper bound for $P_T - P_R$ is 0.01523.

Table 42: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI4

		Test Product		
		Max Irritation Score < 3	Max Irritation Score ≥ 3	Total
Reference	**Max Irritation Score < 3**	174	0	174

Product	Max Irritation Score ≥ 3	1	0	1
	Total	175	0	175

Source: Reviewer's analysis

Table 43: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful Degree of Irritation During the Induction Phase in PPPI4

Hypothesis	Proportion of Test Score ≥ 3 (P_T) (N=176)	Proportion of Reference Score ≥ 3 (P_R) (N=175)	Point Estimate of $P_T - P_R$	One-sided 95% Upper Confidence Limit of $P_T - P_R$
H_0: $P_T - P_R > \delta$ (inferior) H_1: $P_T - P_R \leq \delta$ (non-inferior)	0.0000	0.0057	-0.0057	0.01523

Source: Reviewer's analysis

3.2.10.2.5 Irritation Analysis Results in PPPI5

Table 44 shows the number and percent of applications by induction phase patch number and patch type with a specific combined "dermal response" and "other effects" score in PPPI5. A summary of mean irritation scores during the induction phase in PPPI5 is presented in Table 45.

Table 44: Number (%) of Applications by Induction Phase Patch Number and Patch Type with a Specific Combined "Dermal Response" and "Other Effect" Score in the PPPI5

Patch No: Treatment	Combined "Dermal Response" and "Other Effect" Score Frequency, %							
	0N		1N		2N		3N	
1:Test	172	86.43%	25	12.56%	2	1.01%	0	0.00%
1:Reference	171	85.93%	26	13.07%	2	1.01%	0	0.00%
2:Test	168	84.42%	29	14.57%	2	1.01%	0	0.00%
2:Reference	167	83.92%	30	15.08%	2	1.01%	0	0.00%
3:Test	153	76.88%	39	19.60%	7	3.52%	0	0.00%
3:Reference	155	77.89%	38	19.10%	5	2.51%	1	0.50%
4:Test	154	77.39%	43	21.61%	2	1.01%	0	0.00%
4:Reference	153	76.88%	43	21.61%	3	1.51%	0	0.00%
5:Test	158	79.40%	38	19.10%	3	1.51%	0	0.00%
5:Reference	152	76.38%	44	22.11%	3	1.51%	0	0.00%

6:Test	152	76.38%	46	23.12%	1	0.50%	0	0.00%
6:Reference	156	78.39%	40	20.10%	3	1.51%	0	0.00%
7:Test	150	75.38%	48	24.12%	1	0.50%	0	0.00%
7:Reference	146	73.37%	50	25.13%	3	1.51%	0	0.00%
8:Test	160	80.40%	39	19.60%	0	0.00%	0	0.00%
8:Reference	159	79.90%	39	19.60%	1	0.50%	0	0.00%
9:Test	156	78.39%	42	21.11%	1	0.50%	0	0.00%
9:Reference	156	78.39%	39	19.60%	4	2.01%	0	0.00%

Please refer to Section 3.2.3 for the conversion from letter score to numerical score.
Source: Reviewer's analysis.

Table 45: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI5 per FDA Reviewer

Product	N	Mean (SD)	Min	First Quartile	Median	Third Quartile	Max
A (Test)	199	0.216 (0.333)	0	0	0	0.333	1.444
B (Reference)	199	0.226 (0.354)	0	0	0	0.444	1.667

Source: Reviewer's analysis

The non-inferiority analysis of test patch against the reference patch based on the mean irritation score in PPPI5 using a linear model is shown in Table 46. In the model, the mean irritation score was the response and treatment and subject were fixed effects. The one-sided 95% upper confidence bound was -0.0387 which being negative showed that the test is non-inferior to the reference.

Table 46: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI5 per FDA

Variable	Hypotheses	LSmean Test	LSmean Reference	Estimate of $\mu_A - 1.25*\mu_B$	One-Sided 95% Upper Confidence Bound
Mean Irritation Score	H_0: $\mu_A - 1.25*\mu_B \geq 0$ H_1: $\mu_A - 1.25*\mu_B < 0$	0.2178	0.2218	-0.0595	-0.0387

Source: Reviewer's analysis

The proportion of subjects in PPPI5 with and without a meaningful degree of irritation (at least one irritation score ≥ 3) is cross-tabulated for the test versus reference products in Table 47. A test for non-inferiority of the test patch to the reference patch in terms of proportion of patches with a meaningful degree of irritation in PPPI5 is presented in Table 48. There was no test patch and 1 (00.50%) reference patch with at least one irritation score ≥ 3. The point estimate of $P_T - P_R$, the difference between proportion of test and reference patches with a meaningful degree of irritation is -0.0050 (-0.50%) and the one-sided 95% upper bound for $P_T - P_R$ is 0.01390.

Table 47: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI5

		Test Product		
		Max Irritation Score < 3	Max Irritation Score ≥ 3	Total
Reference Product	Max Irritation Score < 3	191	0	191
	Max Irritation Score ≥ 3	1	0	1
	Total	192	0	192

Source: Reviewer's analysis

Table 48: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful Degree of Irritation During the Induction Phase in PPPI5

Hypothesis	Proportion of Test Score ≥ 3 (P_T) (N=199)	Proportion of Reference Score ≥ 3 (P_R) (N=199)	Point Estimate of $P_T - P_R$	One-sided 95% Upper Confidence Limit of $P_T - P_R$
H_0: $P_T - P_R > \delta$ (inferior) H_1: $P_T - P_R \leq \delta$ (non-inferior)	0.0000	0.0050	-0.0050	0.01390

Source: Reviewer's analysis

3.2.10.2.6 Irritation Analysis Results in PPPI6

Table 49 shows the number and percent of applications by induction phase patch number and patch type with a specific combined "dermal response" and "other effects" score in PPPI6. A summary of mean irritation scores during the induction phase in PPPI6 is presented in Table 50.

Table 49: Number (%) of Applications by Induction Phase Patch Number and Patch Type with a Specific Combined "Dermal Response" and "Other Effect" Score in the PPPI6

Patch No: Treatment	Combined "Dermal Response" and "Other Effect" Score Frequency, %							
	0N		1N		2N		3N	
1:Test	157	86.26%	23	12.64%	2	1.10%	0	0.00%
1:Reference	155	86.11%	24	13.33%	1	0.56%	0	0.00%
2:Test	154	84.62%	26	14.29%	2	1.10%	0	0.00%
2:Reference	149	82.78%	29	16.11%	2	1.11%	0	0.00%
3:Test	139	76.37%	36	19.78%	7	3.85%	0	0.00%
3:Reference	139	77.22%	35	19.44%	5	2.78%	1	0.56%
4:Test	142	78.02%	38	20.88%	2	1.10%	0	0.00%
4:Reference	139	77.22%	38	21.11%	3	1.67%	0	0.00%
5:Test	145	79.67%	34	18.68%	3	1.65%	0	0.00%
5:Reference	141	78.33%	36	20.00%	3	1.67%	0	0.00%
6:Test	138	75.82%	43	23.63%	1	0.55%	0	0.00%
6:Reference	140	77.78%	37	20.56%	3	1.67%	0	0.00%
7:Test	136	74.73%	45	24.73%	1	0.55%	0	0.00%
7:Reference	131	72.78%	46	25.56%	3	1.67%	0	0.00%
8:Test	146	80.22%	36	19.78%	0	0.00%	0	0.00%
8:Reference	144	80.00%	35	19.44%	1	0.56%	0	0.00%
9:Test	143	78.57%	38	20.88%	1	0.55%	0	0.00%
9:Reference	141	78.33%	35	19.44%	4	2.22%	0	0.00%

Please refer to Section 3.2.3 for the conversion from letter score to numerical score.
Source: Reviewer's analysis.

Table 50: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI6 per FDA Reviewer

Product	N	Mean (SD)	Min	First Quartile	Median	Third Quartile	Max
A (Test)	182	0.218 (0.341)	0	0	0	0.333	1.444
B (Reference)	180	0.227 (0.362)	0	0	0	0.444	1.667

Source: Reviewer's analysis

The non-inferiority analysis of test patch against the reference patch based on the mean irritation score in PPPI6 using a linear model is shown in Table 51. In the model, the mean irritation score was the response and treatment and subject were fixed effects. The one-sided 95% upper confidence bound was -0.0394 which being negative showed that the test is non-inferior to the reference.

Table 51: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI6 per FDA

Variable	Hypotheses	LSmean Test	LSmean Reference	Estimate of $\mu_A - 1.25*\mu_B$	One-Sided 95% Upper Confidence Bound
Mean Irritation Score	H_0: $\mu_A - 1.25*\mu_B \geq 0$ H_1: $\mu_A - 1.25*\mu_B < 0$	0.2179	0.2230	-0.0608	-0.0394

Source: Reviewer's analysis

The proportion of subjects in PPPI6 with and without a meaningful degree of irritation (at least one irritation score ≥ 3) is cross-tabulated for the test versus reference products in Table 52. A test for non-inferiority of the test patch to the reference patch in terms of proportion of patches with a meaningful degree of irritation in PPPI6 is presented in Table 53. There was no test patch and 1 (00.56%) reference patch with at least one irritation score ≥ 3. The point estimate of $P_T - P_R$, the difference between proportion of test and reference patches with a meaningful degree of irritation is -0.0056 (-0.56%) and the one-sided 95% upper bound for $P_T - P_R$ is 0.01523.

Table 52: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI6

		Test Product		
		Max Irritation Score < 3	Max Irritation Score ≥ 3	Total
Reference Product	Max Irritation Score < 3	174	0	174
	Max Irritation Score ≥ 3	1	0	1
	Total	175	0	175

Source: Reviewer's analysis

Table 53: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful Degree of Irritation During the Induction Phase in PPPI6

Hypothesis	Proportion of Test Score ≥ 3 (P_T) (N=182)	Proportion of Reference Score ≥ 3 (P_R) (N=180)	Point Estimate of $P_T - P_R$	One-sided 95% Upper Confidence Limit of $P_T - P_R$
H_0: $P_T - P_R > \delta$ (inferior) **H_1: $P_T - P_R \leq \delta$ (non-inferior)**	0.0000	0.0056	-0.0056	0.01523

Source: Reviewer's analysis

3.2.10.2.7 Sensitization Analysis

Table 54, Table 55, Table 56, Table 57, Table 58 and Table 59 show the number and percent of applications by challenge phase evaluation time after patch removal and patch type with a specific dermal response and other effects score in PPPS1, PPPS2, PPPS3, PPPS4, PPPS5 and PPPS6, respectively. The total number of patches is not same at all of the time points because some subjects did not have one or more irritation assessments.

Table 54: Number (%) of Applications by Challenge Phase Evaluation Time and Patch Type with a Specific Combined Dermal Response and Other Effects Score in the PPPS1

Time: Treatment	Total Number of Patches	Combined "Dermal Response" and "Other Effect" Score Frequency, %					
		0N		1N		2N	
30 Minutes: Test	217	185	85.25%	32	14.75%	0	0.00%
30 Minutes: Reference	215	179	83.26%	36	16.74%	0	0.00%
24 Hour: Test	216	208	96.30%	7	3.24%	1	0.46%
24 Hour: Reference	214	203	94.86%	10	4.67%	1	0.47%
48 Hours: Test	214	213	99.53%	0	0.00%	1	0.47%
48 Hours: Reference	212	209	98.58%	2	0.94%	1	0.47%
72 Hours: Test	215	214	99.53%	1	0.47%	0	0.00%
72 Hours: Reference	213	212	99.53%	1	0.47%	0	0.00%

Source: Reviewer's analysis.

Table 55: Number (%) of Applications by Challenge Phase Evaluation Time and Patch Type with a Specific Combined Dermal Response and Other Effects Score in the PPPS2

Time: Treatment	Total Number of Patches	Combined "Dermal Response" and "Other Effect" Score Frequency, %					
		0N		1N		2N	
30 Minutes: Test	191	162	84.82%	29	15.18%	0	0.00%
30 Minutes: Reference	189	156	82.54%	33	17.46%	0	0.00%
24 Hour: Test	191	185	96.86%	5	2.62%	1	0.52%
24 Hour: Reference	189	180	95.24%	8	4.23%	1	0.53%
48 Hours: Test	189	188	99.47%	0	0.00%	1	0.53%

48 Hours: Reference	187	184	98.40%	2	1.07%	1	0.53%
72 Hours: Test	190	189	99.47%	1	0.53%	0	0.00%
72 Hours: Reference	188	187	99.47%	1	0.53%	0	0.00%

Source: Reviewer's analysis.

Table 56: Number (%) of Applications by Challenge Phase Evaluation Time and Patch Type with a Specific Combined Dermal Response and Other Effects Score in the PPPS3

Time: Treatment	Total Number of Patches	Combined "Dermal Response" and "Other Effect" Score Frequency, %					
		0N		1N		2N	
30 Minutes: Test	187	157	83.96%	30	16.04%	0	0.00%
30 Minutes: Reference	186	153	82.26%	33	17.74%	0	0.00%
24 Hour: Test	187	180	96.26%	6	3.21%	1	0.53%
24 Hour: Reference	186	176	94.62%	9	4.84%	1	0.54%
48 Hours: Test	185	184	99.46%	0	0.00%	1	0.54%
48 Hours: Reference	184	181	98.37%	2	1.09%	1	0.54%
72 Hours: Test	185	184	99.46%	1	0.54%	0	0.00%
72 Hours: Reference	184	183	99.46%	1	0.54%	0	0.00%

Source: Reviewer's analysis.

Table 57: Number (%) of Applications by Challenge Phase Evaluation Time and Patch Type with a Specific Combined Dermal Response and Other Effects Score in the PPPS4

Time: Treatment	Total Number of Patches	Combined "Dermal Response" and "Other Effect" Score Frequency, %					
		0N		1N		2N	
30 Minutes: Test	170	142	83.53%	28	16.47%	0	0.00%
30 Minutes: Reference	169	138	81.66%	31	18.34%	0	0.00%
24 Hour: Test	170	164	96.47%	5	2.94%	1	0.59%
24 Hour: Reference	169	160	94.67%	8	4.73%	1	0.59%
48 Hours: Test	168	167	99.40%	0	0.00%	1	0.60%
48 Hours: Reference	167	164	98.20%	2	1.20%	1	0.60%
72 Hours: Test	169	168	99.41%	1	0.59%	0	0.00%

72 Hours: Reference	168	167	99.40%	1	0.60%	0	0.00%

Source: Reviewer's analysis.

Table 58: Number (%) of Applications by Challenge Phase Evaluation Time and Patch Type with a Specific Combined Dermal Response and Other Effects Score in the PPPS5

Time: Treatment	Total Number of Patches	Combined "Dermal Response" and "Other Effect" Score Frequency, %					
		0N		1N		2N	
30 Minutes: Test	192	162	84.38%	30	15.63%	0	0.00%
30 Minutes: Reference	193	159	82.38%	34	17.62%	0	0.00%
24 Hour: Test	192	185	96.35%	6	3.13%	1	0.52%
24 Hour: Reference	193	183	94.82%	9	4.66%	1	0.52%
48 Hours: Test	190	189	99.47%	0	0.00%	1	0.53%
48 Hours: Reference	191	188	98.43%	2	1.05%	1	0.52%
72 Hours: Test	190	189	99.47%	1	0.53%	0	0.00%
72 Hours: Reference	191	190	99.48%	1	0.52%	0	0.00%

Source: Reviewer's analysis.

Table 59: Number (%) of Applications by Challenge Phase Evaluation Time and Patch Type with a Specific Combined Dermal Response and Other Effects Score in the PPPS6

Time: Treatment	Total Number of Patches	Combined "Dermal Response" and "Other Effect" Score Frequency, %					
		0N		1N		2N	
30 Minutes: Test	175	147	84.00%	28	16.00%	0	0.00%
30 Minutes: Reference	174	142	81.61%	32	18.39%	0	0.00%
24 Hour: Test	175	169	96.57%	5	2.86%	1	0.57%
24 Hour: Reference	174	165	94.83%	8	4.60%	1	0.57%
48 Hours: Test	173	172	99.42%	0	0.00%	1	0.58%
48 Hours: Reference	172	169	98.26%	2	1.16%	1	0.58%
72 Hours: Test	174	173	99.43%	1	0.57%	0	0.00%
72 Hours: Reference	173	172	99.42%	1	0.58%	0	0.00%

Source: Reviewer's analysis.

There were 2 patches with an irritation score of at least 2 at 48 or 72 hour evaluation after patch removal in the challenge phase in all six populations (PPPS1-PPPS6). The list of these patches is given in Table 60. Based on the irritation scores in the induction and challenge phases, the reviewer determined that no patches had a potential sensitization response.

Table 60: Patches with Irritation Score ≥ 2 at 48 or 72 Hour Evaluation in Challenge Phase

Subject ID	Treatment*	Irritation Scores at Different Times after Challenge Phase Patch Removal				Max Irritation Score During Induction Phase	Applicant's Determination of Potential Sensitization in the Challenge Phase (Yes, No)	FDA Determination of Potential Sensitization (Yes, No) Based on Irritation Scores
		30 Mins	24 Hrs	48 Hrs	72 Hrs			
(b) (6)	A	1	2	2	1	2	No	No
	B	1	2	2	1	3	No	No

*: A=Test, B=Reference.
Source: Reviewer's analysis

3.3 Evaluation of Study RP-LID-PK001 (Pharmacokinetic and Adhesion Study)

3.3.1 Study Objectives

The primary objectives of this study were:

- To assess the bioequivalence of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus Lidoderm® after a 12-hour application in healthy adult male and female subjects under fasted conditions.
- To assess the apparent dose delivered following application of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus Lidoderm® after a 12-hour application in healthy adult male and female subjects under fasted conditions.
- To assess the patch adhesive performance of a test formulation of lidocaine 5% topical patch versus Lidoderm® after a 12-hour application in healthy adult male and female subjects.

The secondary objective of this study was:

- To assess the safety and tolerability of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus Lidoderm® after a 12-hour application in healthy adult male and female subjects under fasted conditions.

3.3.2 Study Design

This was a single-center, randomized, open-label, single-dose, two-period, crossover study to assess the bioequivalence of a single 2100 mg dose of a test (T) formulation of lidocaine 5% topical patch versus Lidoderm® (RLD) topical patch after a 12-hour application in healthy adult male and female subjects under fasted conditions and to compare adhesive properties of the test and reference patches.

The treatments were the following.

- Test (T): 3 x 700 mg patches of test product (lidocaine 5%)
- Reference (R): 3 x 700 mg patches of reference product (Lidoderm®).

Each subject was randomized to one of two treatment sequences (T-R, R-T) according to a randomization schedule as shown in Table 61. There was a 7-day washout between each patch administration. Subjects were dosed on the same day for Day 1 of Period 1, crossed over to the alternate formulation and were dosed on the same day for Day 8 of Period 2.

Table 61: Randomization Scheme for the Study RP-LID-PK001

Sequence	Period I	Period II
T-R	Test	Reference
R-T	Reference	Test

Following an overnight fast of at least 10 hours, subjects received their assigned treatment at approximately 08:00 hours (± 2 hour) as three topical patches applied simultaneously, for a 12-hour period, to the infrascapular area of the back on either side of the spine, without occlusion, with approximately 2.5 cm between each patch. Patches were applied by qualified study site personnel.

Serial blood samples for determination of lidocaine plasma concentrations and PK analysis were obtained at time 0 (within 90 minutes pre-application) and 1, 1.5, 2, 3, 6, 9, 12, 15, 18, 21, 24 and 48 hours after patch application. Subjects were discharged from the research facility approximately 24 hours after patch application and returned on an out-patient basis for collection of the 48 hour post-dose sample. The study was conducted at a single center (Hackensack, New Jersey).

Subjects could not apply topical products to or wash the back, or engage in strenuous activity during the 12-hour patch application period. Water was allowed *ad-libitum* during the study except for 1 hour prior through 1 hour post-dose. Subjects fasted for at least 4 hour following patch application. Standard meals were provided at approximately 4 and 10 hours after patch application and an evening snack was provided on the evenings of admission and the days of dosing.

If any patch fell off during the study, the date and time it fell off were recorded and a new patch was not applied.

3.3.3 Adhesion Assessments

Patch adhesion was assessed 6 hours (± 30 min) following patch application and within 30 minutes prior to patch removal by qualified study site personnel using the FDA recommended adhesion rating scale below. When a complete patch detachment occurred prior to the time of assessment, the time of detachment was captured. Detached patches were not replaced.

Adhesion Scoring Scale

0 = ≥ 90% adhered (essentially no lift off the skin)
1 = ≥ 75% to <90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to <75% adhered (less than half of the patch lifting off the skin)
3 = >0% to < 50% adhered but not detached (more than half of the patch lifting off the skin but not completely detached)
4 = 0% adhered - patch detached (patch completely off the skin)

3.3.4 Endpoints

Applicant's Primary Endpoint for Adhesion:

The primary endpoint for adhesion was the cumulative adhesion index (mean adhesion score), which was calculated as the sum of a subject's individual patch adhesion scores divided by the number of scores during different time points.

When an individual patch adhesion score was missing due to patch detachment, a patch adhesion score of '4' was imputed for all calculations.

Reviewer's Primary Endpoint for Adhesion:

The reviewer's primary endpoint is the mean adhesion score which is defined for each subject for teach treatment as the mean of the adhesion scores over all patches of that patch type (test or reference) and all evaluation time points (at 6 hours after patch application and before patch removal).

Reviewer's Secondary Endpoint for Adhesion:

- The proportion of subjects with a meaningful degree of detachment (adhesion score ≥ 3 at any time point for any of the three patches of the same type)
- Time from patch application until complete or partial patch detachment
- Proportion of subjects with a mean adhesion score for test patch greater than the mean adhesion score for the reference patch by 1 or more, compared to the proportion of subjects with a mean adhesion score for the reference patch greater than the mean adhesion score for the test patch by 1 or more.

Reviewer's Comments:

1. Each subject had three test patches and three reference patches. The mean adhesion score was defined as the mean of adhesion scores of all three patches of the same type (test or reference) at all evaluation points. The meaningful degree of detachment is defined as any of those three patches of the same type having an adhesion score ≥ 3 at any of the adhesion evaluation time points.

2. The adhesion assessment times were equally spaced. Therefore a simple average of adhesion scores is appropriate as the primary endpoint.

3.3.5 Sample Size Considerations

The applicant determined that 48 subjects would provide sufficient data to meet the primary objectives of this study.

3.3.6 Statistical Methodologies

3.3.6.1 Analysis Populations

Applicant's Analysis Populations:

PK Population:

The PK Population consisted of those subjects who completed both treatments without any major protocol violations, who provided plasma lidocaine concentration data sufficient to estimate PK parameters and had all 3 patches attached for ≥ 11 hours during each period.

Safety Population:

The safety population consisted of those subjects who received at least one dose of study drug.

Reviewer's Analysis Population:

Per Protocol Population for Adhesion (PPPA):

The per protocol population for adhesion includes all patches except those that are removed early for unacceptable irritation or safety or those from the subjects who dropped out of the study before the 12 hour application.

A patch that is completely detached, and not manually removed for the above-mentioned reasons, before the 12-hour patch application period, is included in the PPPA and a score of 4 (complete patch detachment) is carried forward as LOCF for all further assessments for that specific patch.

Reviewer's Comment:

The application used the safety population for analysis of adhesion. There was no separate definition of per protocol population for adhesion. The reviewer agreed with applicant's analysis population for adhesion which was also recommended by FDA's clinical team. In this case all patches from the subjects in the safety population constitute the PPPA.

3.3.6.2 Primary Analysis of Adhesion

Applicant's Analysis Methods:

The cumulative adhesion index was summarized by treatment and time point using descriptive statistics (mean, standard deviation, median, minimum and maximum values). Difference in the cumulative adhesions index between test and reference patches was analyzed using analysis of variance (ANOVA) model including terms for sequence, study treatment, and period as fixed effects, and subject nested within sequence as a random effect.

Frequencies and percentages were used to describe the mean cumulative adhesion scores range at each time point by treatment. The mean cumulative adhesion scores were divided into five groups: '0 -<1', '1-<2', '2-<3', '3-<4' '4'. Individual adhesion scores were summarized by treatment and time point using frequency and percentage. The number of detached patches was summarized using frequency and percentages.

Duration of wear prior to patch detachment was summarized using descriptive statistics. Differences in the time from application until patch detachment between test and reference patches were analyzed using the SAS procedure PROC LIFETEST with the model, time*censor(0) as the time effect and treatment as the strata effect.

When an individual patch adhesion score was missing due to patch detachment, a patch adhesion score of '4' was imputed for all calculations.

Reviewer's Analysis Methods:

To demonstrate adequate product adhesion, the test product should be shown to be statistically non-inferior compared to the reference product based upon evaluation of the difference in the test and reference overall mean adhesion scores, with a non-inferiority (NI) margin of 0.15 (δ = 0.15). The hypotheses for evaluating non-inferiority are:

H0: $\mu_T - \mu_R > \delta$ (not non-inferior)
H1: $\mu_T - \mu_R \leq \delta$ (non-inferior)

where μ_T and μ_R are the mean adhesion scores for treatment and reference, respectively. To demonstrate non-inferiority of the test product to the reference product, the upper bound of the one-sided 95% CI of the difference in mean adhesion score for the test product and the reference product must be less than or equal to 0.15.

For the primary analysis of the primary endpoint, an analysis of variance (ANOVA) was performed in SAS using PROC MIXED, in which the mean adhesion score was treated as the dependent variable, sequence, treatment and period were treated as fixed effects and subject nested in sequence as a random effect.

The proportion of subjects with a meaningful degree of detachment (adhesion score of 3 or greater) is evaluated for each product. The reviewer used the same method for the analysis of binary endpoint (secondary analysis) as in Section 3.2.7.2. Frequency tables showing the number of patches with each adhesion score at each evaluation time point for each treatment are provided.

3.3.7 Subject Disposition and Analysis Populations

The study enrolled 48 subjects. All subjects completed the study and were included in the safety population. Each subject had three test and three reference patches. All patches were included in the analysis population for adhesion (per protocol population for adhesion or PPPA). The determination of analysis populations by the applicant and that by the FDA reviewer are presented in Table 62. The PP population for adhesion recommended by the clinical reviewer matched with that of the applicant.

Table 62: Determination of Analysis Populations per Patch

	Applicant's Determination			FDA's Determination		
	Overall	Test	Reference	Overall	Test	Reference
Enrolled	288	144	144	288	144	144
Safety Population (SP)	288 (100%)	144 (100%)	144 (100%)	288 (100%)	144 (100%)	144 (100%)
Per Protocol Population for Adhesion (PPPA)	288 (100%)	144 (100%)	144 (100%)	288 (100%)	144 (100%)	144 (100%)
Excluded from PP population	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Applicant's datasets and reviewer's analysis

3.3.8 Demographic and Baseline Characteristics

The demographic characteristics of all enrolled subjects (same as the safety population and adhesion analysis population for this study) are shown in Table 63. About half (52%) of the subjects were male. Majority of the subjects were white (60%). Approximately 73% subjects were between age 18 and 40 years, followed by 27% subjects in the age group 41 to 64 years. The mean and median ages were 31.96 and 31.5 years, respectively. The study recruited subjects at one site: Hackensack, NJ.

Table 63: Demographic Characteristics for Study RP-LID-PK001: Gender, Race and Age

		All Enrolled (N=48)
Gender	Female	23 (47.92%)
	Male	25 (52.08%)
Race	Black	19 (39.58%)
	White	29 (60.42%)
Age Group in Years	18-40	35 (72.92%)
	41-64	13 (27.08%)
Age in Years	Mean, SD	31.96, 9.22
	Min, Max	18, 45
	Q1, Median, Q3	22, 31.5, 45

Source: Reviewer's analysis

3.3.9 Results and Conclusions

3.3.9.1 Applicant's Analysis Results

The cumulative adhesion index (mean of the cumulative adhesion score) was calculated as the sum of a subject's individual patch adhesion scores divided by the number of scores during different time points. The cumulative adhesion index was calculated by subject for each treatment and time point and summarized by treatment and time point using descriptive statistics. Differences in the cumulative adhesions index between test and reference patches at each time point were analyzed using analysis of variance (ANOVA) model including terms for sequence, study treatment, and period as fixed effects, and subject nested within sequence as a random effect.

A statistical summary of the cumulative adhesion index and differences in the cumulative adhesion index for test vs. reference formulations for safety population is presented in Table 64.

Table 64: Applicant's Summary of Cumulative Adhesion Index and Differences in the Cumulative Adhesion Index (Test vs. Reference) in Safety Population

	Mean(SD)		Least Square Mean		Mean Test - Reference	90% Confidence Interval (T - R)
Patch Removal	**Test**	**Reference**	**Test**	**Reference**		
6 hours after application	0.333 (0.4673)	0.805 (0.9048)	0.333	0.805	-0.472	(-0.686, -0.258)
Within 30 min prior to patch removal	0.722 (0.8847)	1.514 (1.2922)	0.722	1.514	-0.792	(-1.066, -0.518)
Combined	0.528 (0.6563)	1.160 (1.0539)	0.528	1.160	-0.632	(-0.862, -0.402)

Source: Clinical Study Report, Study RP-LID-PK001, Table 11-4

Reviewer's Comments:

1. It should be noted that the rightmost column of Table 11-4 in the clinical study report has a column heading "90% Confidence Interval (T/R)". After checking the source Table 14.5.4 in the clinical study report and the SAS code that generated that table, the reviewer concluded that the rightmost column heading in Table 11-4 is incorrect. It should be "90% Confidence Interval (T - R)". Table 64 shows the correct column heading.

2. There was one patch where the adhesion score decreased from the 6 hour assessment to 12 hour assessment. The applicant did not adjust the adhesion score for that patch in the analysis.

3.3.9.2 Reviewer's Analysis Results

The adhesion scores for each patch should be monotone over time. It is observed that out of a total of 288 patches in the PP population, one patch did not satisfy monotonicity of the adhesion scores. The reviewer performed the analyses by monotonizing the adhesion scores where at each time point the adhesion score of a patch is replaced by the highest adhesion score of the previous assessments if the current adhesion score is observed to be less than the adhesion score at any of the previous time points. This method is also known as the worst observation carried forward (WOCF). Table 65 shows the number of patches with imputed adhesion scores in the PPPA.

The frequency distribution of monotonized adhesion scores by treatment at each assessment time point is presented in Table 66.

Table 65: Number of Patches with Imputed Adhesion Scores in the PPPA

	Test	Reference
Randomized		

Number of patches	144		144	
FDA's PP for Adhesion				
Number of patches	144		144	
Total N of patches with worst observation carried forward, N (%)	0	(0.00%)	1	(0.69%)
Due to patch fell off /complete detachment (%)	0	(0.00%)	0	(0.00%)
Due to improved adhesion score recorded*, N (%)	0	(0.00%)	1	(0.69%)
Due to missing intermittent adhesion score, N (%)	0	(0.00%)	0	(0.00%)

* Reference: Subjec (b) (6), Patch # 1
Source: Reviewer's Analysis

Table 66: Number and Percent of Test and Reference Patches with Each Monotonized Adhesion Score at Each Assessment

Assessment Time	Treatment	Adhesion Score									
		0		1		2		3		4	
6 Hours	**Test**	109	(75.69%)	24	(16.67%)	9	(6.25%)	2	(1.39%)	0	(0.00%)
	Reference	79	(54.86%)	38	(26.39%)	9	(6.25%)	12	(8.33%)	6	(4.17%)
12 Hours	**Test**	86	(59.72%)	32	(22.22%)	11	(7.64%)	10	(6.94%)	5	(3.47%)
	Reference	44	(30.56%)	40	(27.78%)	22	(15.28%)	17	(11.81%)	21	(14.58%)

Source: Reviewer's analysis

A summary of mean monotonized adhesion scores is presented in Table 67. The non-inferiority analysis of test patch against the reference patch based on the mean monotonized adhesion score using a linear mixed model is presented in Table 68. This analysis will be considered as the primary analysis. In the model the mean monotonized adhesion score was the response variable, sequence, treatment and period were fixed effects and subject nested in sequence was a random effect. The mean monotonized adhesion score was calculated for each patch type for each subject. The upper one-sided 95% confidence bound for test mean – reference mean is -0.4075 which being less than the chosen margin 0.15 showed that the test is non-inferior to the reference with respect to adhesion.

Table 67: Summary of Mean Adhesion Scores (Monotonized) in the PP Population per FDA Reviewer

Product	N	Mean (SD)	Min	First Quartile	Median	Third Quartile	Max
Test	48	0.528 (0.656)	0	0	0.250	0.833	2.500
Reference	48	1.163 (1.055)	0	0.333	0.917	2.000	3.667

Source: Reviewer's analysis

Table 68: Primary Non-inferiority Analysis of Mean Adhesion Score (Monotonized) for Test vs. Reference Patches per FDA

Variable	Hypotheses	LSmean Test	LSmean Reference	Estimate of	One-Sided 95% Upper Confidence

		(SE)	(SE)	$\mu_T - \mu_R$	Bound
Mean Adhesion Score	H_0: $\mu_T - \mu_R > \delta$ H_1: $\mu_T - \mu_R \leq \delta$	0.5278 (0.1257)	1.1632 (0.1257)	-0.6354	-0.4075

Source: Reviewer's analysis

As an additional analysis, the reviewer constructed using the same model a 95% one-sided confidence interval for the difference $\mu_T - 1.25*\mu_R$ which can be used to test the following non-inferiority hypotheses.
H_0: $\mu_T - 1.25*\mu_R > 0$
H_1: $\mu_T - 1.25*\mu_R \leq 0$.

The results of that non-inferiority analysis are presented in Table 69. Since Table 69 shows that the upper bound of the one-sided 95% confidence bound is less than 0, the test product could be considered to be non-inferior to the reference product.

Table 69: Additional Non-inferiority Analysis of Mean Adhesion Score (Monotonized) for Test vs. Reference Patches per FDA

Variable	Hypotheses	LSmean Test (SE)	LSmean Reference (SE)	Estimate of $\mu_T - 1.25*\mu_R$	One-Sided 95% Upper Confidence Bound
Mean Adhesion Score	H_0: $\mu_T - 1.25* \mu_R > 0$ H_1: $\mu_T - 1.25*\mu_R \leq 0$	0.5278 (0.1257)	1.1632 (0.1257)	-0.0262	-0.6663

Source: Reviewer's analysis

The proportion of subjects in PPPA with and without a meaningful degree of detachment (at least one adhesion score ≥ 3) is cross-tabulated for the test versus reference products in Table 70. A test for non-inferiority of the test patch to the reference patch in terms of proportion of subjects with a meaningful degree of detachment in the PPPA is presented in Table 71. There were 11 out of 48 (22.92%) subjects with at least one adhesion score of test patches ≥ 3 and 18 out of 48 (37.5%) subjects with at least one adhesion score of reference patches ≥ 3. The point estimate of $P_T - P_R$, the difference between proportion of subjects with a meaningful degree of detachment in test and reference patches is -0.1458 and the one-sided 95% upper bound for $P_T - P_R$ is -0.06603. The time from patch application until complete (score=4) or partial (score ≥ 3) patch detachment is presented in Table 72.

Table 70: Subjects With or Without Meaningful Degree of Detachment (Maximum Adhesion Score ≥ 3 or < 3) for Test and Reference Products in FDA's PPPA

		Test Product		
		Max Adhesion Score < 3	**Max Adhesion Score ≥ 3**	**Total**
Reference Product	**Max Adhesion Score < 3**	27	3	30
	Max Adhesion Score ≥ 3	10	8	18

	Total	37	11	48

Source: Reviewer's analysis

Table 71: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful Degree of Detachment in FDA's PPPA

Hypothesis	Proportion of Subjects with Test Score ≥ 3 (P_T) (N=48)	Proportion of Subjects with Reference Score ≥ 3 (P_R) (N=48)	Point Estimate of $P_T - P_R$	One-sided 95% Upper Confidence Limit of $P_T - P_R$
H_0: $P_T - P_R > \delta$ (inferior) **H_1: $P_T - P_R \leq \delta$ (non-inferior)**	0.2292	0.3750	-0.1458	-0.06603

Source: Reviewer's analysis

Table 72: Time from Patch Application until Patch Complete or Partial Detachment in FDA's PPPA

	Treatment	Time in Hours from Patch Application to Detachment	
		6	12
Patch Complete Detachment (Score = 4)	Test (N=144)	0	5
	Reference (N=144)	6	15
Patch Partial Detachment (Score ≥ 3)	Test (N=144)	2	13
	Reference (N=144)	18	20

Source: Reviewer's analysis

All 48 subjects had all 6 patches in the PPPA. One subject had the treatment mean adhesion score greater than the reference mean adhesion score by more than one while 13 subjects had reference mean adhesion score greater than the test mean adhesion score by more than one. The results are presented in Table 73.

Table 73: Number and Percent of Subjects with Absolute Difference in Mean Adhesion Score Between the Test and Reference Patches Larger Than 1

Categories	Number (%) of Subjects (N=48)
Mean adhesion score for test patch - Mean adhesion score for reference patch >1	1 (2.08%)
Mean adhesion score for reference patch -Mean adhesion score for test patch >1	13 (27.08%)

Source: Reviewer's analysis

3.4 Evaluation of Safety

For a detailed safety evaluation, please refer to the clinical review of this application.

4 SUMMARY AND CONCLUSIONS

This review is based on two studies, RP-LID-SSI and RP-LID-PK001. Study RP-LID-SSI was a randomized, single-center, controlled, evaluator-blinded study to evaluate the potential for skin irritation and sensitization of a test lidocaine 5% transdermal patch compared to the reference Lidoderm® 5% lidocaine patch in healthy adult subjects. The study enrolled 248 healthy adult subjects at a single center (b) (4) in USA. The study had two phases: irritation/induction (Days 1-22) and sensitization/challenge (Days 36-41). Each subject was to receive both patches simultaneously on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the induction phase and on Day 36 during the challenge phase. Skin irritation was assessed using 'dermal response' and 'other effects' scores after each patch removal during the induction phase, and 30 minutes and 24, 48 and 72 hours after patch removal on Day 38. Primary evaluation of irritation was based on non-inferiority analysis of mean irritation score of the test patches against that of the reference patches during the induction phase. Evaluation of sensitization was based on the irritation scores during the challenge phase. The first subject was enrolled o (b) (6) and the last subject completed the study o (b) (6)

Study RP-LID-PK001 was a single-center, randomized, open-label, single-dose, two-period, crossover study to assess the bioequivalence of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus reference Lidoderm® topical patch after a 12-hour application in healthy adult male and female subjects under fasted conditions and to compare adhesive properties of the test and reference patches. The study enrolled 48 subjects at a single center (b) (4) in USA. Each subject was randomized to one of two treatment sequences. In each study period, three test or three reference patches were applied simultaneously, for a 12-hour period, to the infrascapular area of the back on either side of the spine, without occlusion, with approximately 2.5 cm between each patch. Serial blood samples for determination of lidocaine plasma concentrations and PK analysis were obtained at time 0 (within 90 minutes pre-application) and 1, 1.5, 2, 3, 6, 9, 12, 15, 18, 21, 24 and 48 hours after patch application. Patch adhesion was assessed 6 hours (± 30 min) following patch application and within 30 minutes prior to patch removal using the FDA recommended 5-point adhesion rating scale. Primary evaluation of adhesion was based on non-inferiority analysis of mean adhesion score of the test patches against that of the reference patches. The study started on August 22, 2013 and the last subject completed the study on September 18, 2013.

4.1 Summary Tables for the Clinical Reviewer

Table 74: Irritation and Sensitization Analyses (Study RP-LID-SSI) Per Applicant and FDA

	Applicant		FDA											
	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]	Test[1]	Reference[2]
Irritation Analysis PP Population	Applicant's FIAP		PPPI1		PPPI2		PPPI3		PPPI4		PPPI5		PPPI5	
Variable	CII[3]		MIS[4]		MIS[4]		MIS[4]		MIS[4]		MIS[4]		MIS[4]	
Number of Patches	228	228	222	222	196	196	193	192	176	175	199	199	182	180
Mean	0.211	0.212	0.206	0.210	0.209	0.214	0.220	0.224	0.223	0.227	0.216	0.226	0.218	0.227
SD	0.354	0.344	0.323	0.345	0.341	0.354	0.336	0.350	0.345	0.360	0.333	0.354	0.341	0.362
Upper 95% UCB[5] for Test –Reference[6]	0.015													
Upper 95% UCB[5] for Test - 1.25*Reference[7]	-0.034		-0.038		-0.038		-0.039		-0.041		-0.039		-0.039	
Conclusion: Is Test Non-Inferior to Reference?	Yes		Yes		Yes		Yes		Yes		Yes		Yes	
Sensitization Analysis PP Population	Applicant's FSAP		PPPS1		PPPS2		PPPS3		PPPS4		PPPS5		PPPS5	
Number of Patches	225	225	217	215	191	189	187	186	170	169	192	193	175	174
Number of Sensitization	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[1]Test: Lidocaine 5% topical patch (Distributed by Rhodes Pharmaceuticals L.P. and manufactured by Altergon, Italia)

[2]Reference: Lidoderm® (lidocaine patch 5%) (manufactured b [redacted] (b) (4) for Endo Pharmaceuticals, Inc.)

[3]CII: Cumulative Irritancy Index defined by the applicant as the mean of the irritation scores (dermal response + other effects) during the induction phase. Applicant's other effects scale is different from FDA's.

[4]MIS: Mean irritation score is the mean of the 9 irritation scores (dermal response + other effects) during the induction phase.

[5]UCB=Upper Confidence Bound
[6]Applicant's non-inferiority criterion: 95% UCB for Test – Reference <0.11; [7]FDA's non-inferiority criterion: 95% UCB for Test – 1.25*Reference <0.

Table 75: Adhesion Analysis (Study RP-LID-PK001) Per Applicant and FDA

	Applicant		FDA	
	Test	Reference	Test	Reference
Adhesion Analysis Population	Safety		PPPA (Same as Safety)	
Variable	Mean Adhesion Score[1]		Mean Adhesion Score with Highest Observation Carried Forward[2]	
Statistical Method	Linear Mixed Model		Linear Mixed Model	
Number of Subjects	48	48	48	48
Number of Patches	144	144	144	144
Mean	0.528	1.160	0.528	1.163
SD	0.6563	1.0539	0.656	1.055
95% UCB[3] for Test - Reference	-0.402		-0.4075	
Conclusion: Is Test Non-Inferior to Reference?	Yes		Yes	

[1]Applicant's mean adhesion score is the mean of the adhesion scores at 6 and 12 hours after application.
[2]FDA's mean adhesion score is the mean of the adhesion scores at 6 and 12 hours after application. The highest observation is carried forward.
[3]UCB=Upper Confidence Bound

4.2 Statistical Issues

Issues About Study RP-LID-SSI:

1. The quality of the submitted data in this application was extremely poor. There were numerous inconsistencies within and between datasets. The datasets contained incomplete information and many errors. Some of the errors were revealed by the applicant only after FDA asked for information or clarification about inconsistencies in the datasets in Easily Correctable Deficiency (ECD) letters. There are likely many more undetected errors in the datasets. Following are some examples.
    a. The irritation and sensitizations analysis populations and reasons for exclusion from the analysis populations did not match between originally submitted datasets and the datasets submitted on December 9, 2016 in response to an ECD.
    b. The adhesion score for a detached patch should be 4 based on the adhesion scale used in the study. The patch detachment flag and adhesion score were not consistent in the dataset q4-oct16.xpt submitted on December 9, 2016 (please see Table 11).

c. According to the original submission the test patch of Subject (b) (6) and the reference patches of Subjects (b) (6) detached during the challenge phase. However, as shown in Table 10, based on the December 9, 2016 submission, the test patches of Subjec (b) (6) and the reference patch of Subject (b) (6) detached during the challenge phase. These conflicting data give an indication of a possibility of reversing the test and reference data for some or all subjects in the dataset. If that happened, all analyses would be wrong. This gives a strong reason why inconsistent data should never be considered for an approval.
d. In the response to the statistical reviewer's request sent in an ECD letter, the applicant provided a list of patches that were detached and if a replacement patch was applied within 24 hours after detachment. The reviewer found out that for some subjects with detached patches in the list there was no information about detached patches in the data whereas the data contained the same information as the list for some other subjects. When the reviewer pointed it out in another ECD letter to the applicant, the applicant agreed that the dataset did not have the correct information and resubmitted the patch adhesion dataset.
e. The reviewer asked for clarification about a discrepancy that the patch removal date and time did not match between ex.xpt and adph.xpt for some subjects. The applicant admitted the mistake and resubmitted the latter dataset.

2. Some data definition files did not have sufficient documentation and were not clear. Specifically, the variables AVAL and AVLC for each parameter in an ADaM dataset must be clearly defined. However, the data definition files did not have them. The applicant updated some data definition files in response to an FDA request for clarification of those variables for all parameters.

3. The information provided in some ECD responses was wrong or incomplete. Following are some examples.
    a. In response to an ECD letter, the applicant submitted a list subjects with detached patches. However, the reviewer found out that there were subjects with detached patches in the dataset that were not included in the list. When the reviewer pointed it out in a subsequent ECD letter to the applicant, the applicant replied that the subjects who had not completed the study were not included in that list. It appears that the applicant assumed that only the subjects that they thought would be included in the primary analysis had useful information. This is contrary to the good clinical practice.
    b. The reviewer noticed that the list of detached patches that the applicant provided in response to an ECD letter included a subject with detached patches that did not have any detached patches according to the data. When the reviewer pointed it out in another ECD letter to the applicant, the applicant admitted that the subject was included in the list erroneously.

4. Subjects (b) (6) withdrew from the study during the induction phase. In the dataset submitted on December 9, 2016, these subjects were correctly excluded from the PPPI but included in the PPPS without any explanation.

5. Subjec (b) (6) completed the induction phase but was discontinued from the study by the investigator before the challenge phase. However, both patch types were included in the PPPS by the applicant in the dataset submitted on December 9, 2016.

6. The applicant did not submit the case report forms for Subjects (b) (6). Also the submitted case report forms contained many errors such as placing the irritation assessment date and score for one patch at a place designated for another patch. For example, the irritation assessment for the first set of patches was not done for Subject (b) (6) but the assessment date and scores were not left blank for that patch and the irritation assessment information for the second set of patches was placed at that place instead. Additionally, the case report forms had too many data clarification forms attached which not only shows the data collection and recording problems in the first place, it also makes the data prone to inaccuracy. This resulted in additional pages of protocol deviations where new protocol deviations are identified along with the already reported ones. The arrangement of these pages is not clearly explained by the applicant.

7. For Subject (b) (6), the irritation assessments on Da (b) (6) and Da (b) (6) were done 9 and 8 minutes, respectively, after patch removal. The case report form contains comments that these are out-of-window irritation assessments according to the protocol. According to the protocol (Section 4), skin irritation assessments were to occur within 15-30 minutes following removal of each patch during induction phase. Therefore, the comments about out-of-window irritation assessments during the induction phase in the CRF are not consistent with the protocol.

8. According to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion score of 3) during the induction phase, the skin irritation assessment for that patch was not to be included in the irritation analysis and the subject was to be scheduled for a make-up patch application. The protocol did not state if a make-up patch would be applied for the patches that completely detached (adhesion score of 4). However, make-up patches were applied for subjects who did not have any patch adhesion score of 3. It was noted as a protocol deviation by the applicant. However, the applicant did not adjust the analysis populations due to this deviation.

9. The Office of Study Integrity and Surveillance (OSIS) inspection report identified 12 subjects having an adhesion score of 4 (detached) and having a make-up patch. However, Table 14 identifies many more subjects with make-up patches that were intended to replace the irritation scores of detached patches.

10. The OSIS inspection report states that except Subject (b) (6), in other subjects who had a make-up patch for a detached patch, the inspection verified that the replacement patch had been detached for less than 24 hours. However, based on the data submitted on December 9, 2016, the reviewer could not confirm this. All patch detachment times were reported in the dataset as observed times as opposed to the actual times of detachment. In addition, the OSIS report is a direct contradiction to the ECD

response submitted by the applicant on October 21, 2016. In response to Question 2 of the ECD letter, the applicant provided the following list of subjects who had detached patches for which date and time of detachment were unknown:

(b) (6)

This list includes all 10 subjects (b) (6)) for which the OSIS report claimed to have verified that the patch had been detached for less than 24 hours. Since for none of those subjects the time difference between the application time of the patch that detached and the application time of the next patch or a replacement patch is less than 24 hours, the OSIS report's verification claim is inaccurate unless the applicant submitted wrong information in the ECD response and wrong datasets.

11. The OSIS inspection report identified only two subjects (b) (6) who would not have had nine irritation assessments if the make-up patches were not used. However, this review identified many more such subjects. Please refer to Table 9 for detached patches and Table 14 for make-up patches. It appears from the OSIS report that one of the reasons for excluding these subjects from the per protocol analysis is that these subjects have cumulative irritancy index (mean irritation score) greater than zero. The information about whether the cumulative irritancy index is greater than zero is irrelevant in this case. All subjects by this protocol deviation would be affected and affect the results in the same way no matter what the cumulative irritancy index is.

12. According to the protocol, if three patches of a subject were moved or removed for unacceptable degree of irritation during the induction phase, the subject was to be excluded from both the irritation and sensitization analyses of the product, and discontinued from study participation. However, FDA guidance recommends including those subjects in the irritation analysis using last observation carried forward (LOCF). No subject was discontinued due to excessive irritation in this study.

13. According to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion score of 3) during the induction phase, the skin irritation assessment for that patch was not to be included in the irritation analysis and the subject was to be scheduled for a make-up patch application. It is understood that the irritation score from a make-up patch would replace the irritation score of the patch that was <50% adhered but not detached if only a single patch out of 9 patches had <50% adherence without being detached. However, the protocol did not state how the irritation scores would be used when two or more patches of the same type for the same person had <50% adherence without being detached. In response to an ECD (ECD letter date: September 16, 2016, ECD response date: September 29, 2016), the applicant stated that when there were multiple patches of the same type with an adhesion score of 3 for the same subject, a

single make-up patch was applied and the irritation score for the make-up patch replaced the irritation scores of all the patches with an adhesion score of 3 that the make-up patch replaced. The applicant adjusted the number of irritation assessments by counting the number of patches not having an adhesion score of 3 and adding one for the make-up patch to that count. For example, if there are 3 patches with an adhesion score of 3, then the number of irritation scores used to calculate the mean would be 6+1=7. In the reviewer's opinion, this is not an appropriate method to calculate the mean irritation score since it essentially reduces the number of irritation scores unless there is only one patch with an adhesion score of 3. The particular patch type for that subject should be excluded from the irritation and sensitization analyses.

14. The study design did not follow the Draft Guidance on Lidocaine. According to the guidance, patches should be applied on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the induction phase. The patches should be assessed for irritation after patch removal and before new patch application. Patches applied on Day 19 should be assessed on Day 22. Based on the protocol, the subjects were allowed to skip a visit and keep the patches on until the next visit when they were evaluated for skin irritation. It resulted in having the same patch on for 4 or 5 days before an irritation assessment while the patches without a skipped visit were on for 2 or 3 days before the irritation assessment.

15. According to the protocol, the subjects who did not return for one visit to the study site during the induction phase were instructed to keep the patches in place. They were scheduled to receive a make-up patch application at the last visit during the induction phase. The study report did not clearly differentiate the dual use of the terminology "make-up patch" for two different purposes. In the first case, the irritation score of the make-up patch is intended to replace the irritation score of a partially detached (<50% adhesion but not completely detached) patch. In the second case, the make-up patch is simply intended to be an additional patch when a visit was skipped to make a total of 9 patches during the induction phase.

16. According to the protocol, a subject who missed the ninth assessment but had 9 patch applications was considered to have completed the induction phase, and the last observed irritation score (the irritation score for the eighth patch) was carried forward. This approach contradicts the Draft Guidance on Lidocaine since the guidance requires application and evaluation of all 9 patches unless the patch removal is due to excessive irritation. In the reviewer's opinion the subjects who missed the ninth assessment should be excluded from the irritation and sensitization analyses.

17. The protocol specified that hypoallergenic tape would be applied to all four edges of each patch. However, there was no mention of this reinforcement tape in the clinical study report. In response to an ECD (ECD letter date: August 23, 2016, ECD response date: September 6, 2016), the applicant confirmed that the hypoallergenic tape was used on all four edges and diagonally on all patches.

18. The applicant used a different rating scale for "other effects" than what is recommend by FDA in Draft Guidance on Lidocaine. Although the other effects categories are identical between the applicant's and FDA's scales, the numerical values associated with the categories based on the applicant's scale are higher with a wider range than those based on the FDA's scale. The applicant did not use any letter score for the other effects. The other effects rating scales based on the applicant and FDA are presented side by side in Table 4. The applicant's other effects rating scale increases the irritation score (dermal response score + other effects score). This increased irritation score makes both the numerator and denominator of the test statistic, which is a ratio (Test/Reference), larger and thus the ratio closer to one numerically. Therefore, the test is more likely to be found non-inferior to the reference with the applicant's rating scale. The reviewer used the FDA-recommended scale for the analyses of irritation and sensitization.

19. According to the Draft Guidance on Lidocaine, the applicant should provide a frequency table showing the number of applications of each test article with each combined dermal response and other effects score using the last observation carried forward (LOCF) for subjects who discontinued a test article because of unacceptable irritation. The applicant did not provide any such table.

20. The Draft Guidance on Lidocaine states the following: "To demonstrate non-inferiority of the test product compared to the RLD with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score must be less than or equal to 0." However, the applicant's criterion for non-inferiority in the primary analysis was different. The applicant considered the test product to be non-inferior to the reference product if the upper bound of the one-sided 95% confidence interval of the difference between the products (test - reference) was not greater than 0.11. The applicant did not provide any justification in the protocol, statistical analysis plan or clinical study report for its criterion for non-inferiority in the primary analysis and how they determined the non-inferiority margin of 0.11.

Issues About Study RP-LID-PK001:

3. It should be noted that the rightmost column of Table 11-4 in the clinical study report has a column heading "90% Confidence Interval (T/R)". After checking the source Table 14.5.4 in the clinical study report and the SAS code that generated that table, the reviewer concluded that the rightmost column heading in Table 11-4 is incorrect. It should be "90% Confidence Interval (T - R)". Table 64 shows the correct column heading.

4. There was one patch where the adhesion score decreased from the 6 hour assessment to 12 hour assessment. The applicant did not adjust the adhesion score for that patch in the analysis.

4.3 Collective Evidence

In Study RP-LID-SSI, the test patch showed non-inferiority to the reference patch with respect to mean irritation score in the induction phase in six different irritation analysis populations (one-sided 95% upper confidence bound for Test -1.25*Reference using a linear model based on reviewer's analysis: -0.038 in two of the irritation analysis populations, -0.039 in three of the irritation analysis populations and -0.041 in one irritation analysis population). No patch had a potential sensitization. In Study RP-LID-PK001, the test patch showed non-inferiority to the reference patch with respect to mean adhesion score (one-sided 95% upper confidence bound for Test - Reference using a linear mixed model based on reviewer's analysis: -0.4075).

4.4 Conclusions and Recommendations

The applicant submitted results from two studies - an irritation and sensitization study (Study RP-LID-SSI) to evaluate the potential for skin irritation and sensitization of a test lidocaine 5% transdermal patch compared to the reference Lidoderm® 5% lidocaine patch in healthy adult subjects and a pharmacokinetic and adhesion study (Study RP-LID-PK001) to assess the bioequivalence of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus reference Lidoderm® topical patch after a 12-hour application in healthy adult male and female subjects under fasted conditions and to compare adhesive properties of the test and reference patches. The irritation and sensitization study RP-LID-SSI had numerous issues with the design, conduct and data quality. Due to design and conduct issues and inconsistencies within and between datasets, no single analysis population could be considered. The reviewer considered six different irritation analysis populations and six different sensitization analysis populations. The test patch showed non-inferiority to the reference patch with respect to mean irritation score in the induction phase in all of those irritation analysis populations. There was no sensitization reaction in any of the sensitization analyses. However, considering the extremely poor quality of data, the reviewer has no confidence in the correctness of the results. In the adhesion study RP-LID-PK001, the test patch showed non-inferiority to the reference patch with respect to mean adhesion score in the per protocol population.

References:

1. McNemar Q, Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika* 1947; 12(2): 153-157.
2. Schuirmann, DJ, One-sided Tests and Confidence Bounds for the Difference between Probabilities for Matched Pairs Dichotomous Data. Presented at the Spring Meetings of the Eastern North American Region (*ENAR*) of the International Biometric Society, March 17, 2008 in Crystal City, VA.
3. Nam JM, Establishing equivalence of two treatments and sample size requirements in matched-pairs design. *Biometrics* 1997; 53(4): 1422-1430.
4. Liu JP, Hsueh HM, Hsieh E, and Chen JJ, Test for equivalence or non-inferiority for paired binary data. *Statistics in Medicine* 2002; 21: 231-245.

Somesh Chattopadhyay

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Fairouz Makhlouf

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Stella Grosser

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

OTHER REVIEW(s)

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: December 8, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director,
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Clinical inspection at [redacted] (b) (4) covering ANDA 209190

Inspection Summary:

At the request of the Office of Study Integrity and Surveillance (OSIS), the Office of Regulatory Affairs (ORA) conducted an inspection of the clinical portion of **study RP-LID-SSI** conducted at [redacted] (b) (4) An additional bioequivalence study (**RP-OX-PK005**) was selected for review from the firm's master list for surveillance assessment. Based upon the results of this inspection, we recommend that clinical data from study RP-LID-SSI be accepted for Agency review, except for **subjects** [redacted] (b) (6). For further details, please see the OSIS evaluation section under **Observation 2**.

Studies audited during this inspection:

Study Number: RP-LID-SSI (ANDA 209190)
Study Title: "A Randomized, Controlled Study to Evaluate the Skin Irritation and Sensitization Potential of

a Test Lidocaine 5% Topical Patch Compared to Lidoderm 5% Topical Patch Using a Repeat Insult Patch Test Design in Healthy Adults"

Study Dates: Group 1: August 20, 2013 through September 29, 2013; Group 2: November 11, 2013 through December 15, 2013

Study Number: RP-OX-PK005 (unknown submission status, sponsored by Rhodes)

Study Title: "A Randomized, Open-Label, Three Period, Crossover, Single-Dose, Comparative Bioavailability and Bioequivalence Study of Oxycodone Hydrochloride Immediate Release Tablets and Roxicodone in Healthy Adults under Fasted Conditions"

Study Dates: December 7, 2015 through December 23, 2015

ORA Investigator Peter Lenahan conducted the inspection of clinical portions of these studies from October 17, 2016 through October 25, 2016.

The audit included a thorough review of the facility and equipment, protocols, Institutional Review Board (IRB) documents, monitoring activities, training records, study personnel, test article accountability and integrity, current SOPs, study records and correspondence, adverse event reporting, and quality assurance.

At the conclusion of the inspection, Form FDA-483 was issued (**Attachment 1**). We received a written response to FDA-483 observations from (b) (4) dated November 7, 2016 (**Attachment 2**). The FDA-483 observations, Frontage's responses, and our evaluation of the observations and responses follow.

(b) (4)

(b) (4)

OSIS Evaluation:

We find (b) (4) response satisfactory. (b) (4)

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

OSIS Evaluation:

We find [redacted] (b) (4) acknowledgement and corrective actions satisfactory. Email communication within Frontage on 8/27/2013 documented that there was confusion regarding how to handle make-up patches for subjects with suboptimal adherence scores (**Exhibit 9**). Additional email communication between Frontage and the Sponsor on 9/11/2013 indicated that the Sponsor was aware that subjects with adhesion scores of 3 or greater were receiving make-up patches (**Exhibit 9**). Despite these communications, the protocol deviation was not acknowledged until a data review conducted three years after study completion. New provisions in the revised SOP should prevent similar oversights from happening in the future.

Upon review of Study Subjects notes for the 12 affected subjects (**Subject ID #'s: 1013, 1025, 1058, 1095, 1098, 1156, 1164, 1166, 1177, 1185, 1201, and 1206**) we confirmed that subjects had complete patch detachment and were given an adhesion score of 4 (**Exhibit 10**). All 12 subjects, despite being given a make-up patch against protocol, were treated and assessed consistently. In all subjects except two (**Subjects 1095 and 1206**), we could also verify that patches had been completely detached for less than 24 hours, thus maintaining irritation and sensitization assessment eligibility. **Subjects 1095 and 1206** were unaware of when the patch became fully detached (**see pages 16 and 58 of Exhibit 10**), and thus, there was no assurance of whether the patch had been off for over 24 hours. Both subjects had a cumulative irritancy index of 0; however, if the patch were detached for more than 24 hours, the irritation score may be incorrectly low. Thus, the cumulative irritation index may not be accurate.

Of the 12 subjects affected by the protocol deviation, only two (**Subjects 1177 and 1201**) had a cumulative irritancy index greater than 0 (**subject 1177, CII = 0.89; subject 1201, CII = 0.78; see CRFs - Exhibits 11 and 12**). The decision to give these subjects make-up patches despite having fully detached patches altered the total number of skin irritation assessments from eight to nine. The protocol states that "Subjects must have a minimum of 9 patch applications during the Induction Phase." Thus, **subjects 1177 and 1201** would not have had the appropriate number of irritation assessments to be included in the per protocol analysis.

Recommendation:

Following review of clinical data for **study RP-LID-SSI**, the Form FDA 483 observations, and the response received from [redacted] (b) (4) we recommend that clinical study data be accepted for further Agency review. However, we recommend that data from **subjects** [redacted] (b) (6) be excluded from per protocol analysis due to a protocol deviation. The cumulative irritancy index for **subjects** [redacted] (b) (6) may not be accurate due to the inability to confirm whether a patch was fully detached for greater than 24 hours. Irritation and sensitization data from **subjects** [redacted] (b) (6) **and** [redacted] (b) (6) would not have been eligible for per protocol analysis had the protocol been followed as written.

This inspection covered an irritation/sensitization study, and as such, it was not conducted as a typical surveillance inspection reviewing multiple applications. There were also no recent or ongoing additional irritation/sensitization studies at Frontage to assess. However, study **RP-OX-PK005** (Bioequivalence, submission status unknown) was selected from the firm's master study list, and no objectionable conditions were observed with this study.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Final Classification:

[redacted] (b) (4)

CC:
OTS/OSIS/Kassim/Taylor/Haidar/Fenty-Stewart/Nkah/Miller/Kadavil
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala
OTS/OSIS/DGDBE/Cho/Murphy/Skelly/Choi/Au/Scheibner
Draft: KAS 12/05/2016
Edit: MFS 12/5/2016; SJC 12/6/2016
OSIS file #: BE7221
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites [redacted] (b) (4)
FACTS: [redacted] (b) (4)

Kara A. Scheibner -S
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA 209190

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your amendment received on February 27, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is May 26, 2020.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Andrew Potter, Regulatory Project Manager, at (240) 402 - 9266.

Sincerely,

{See appended electronic signature page}

Andrew Potter
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Andrew
Potter

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Date: 3/03/2020 07:49:42AM
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ANDA 209190

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your amendment received on July 30, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a standard major amendment. If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is March 29, 2020. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is May 29, 2020.

If you have any questions, contact Andrew Potter, Regulatory Project Manager, at (240) 402 - 9266.

Sincerely,

{See appended electronic signature page}

Andrew Potter
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Andrew
Potter

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Date: 7/31/2019 08:21:26AM
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ANDA 209190

COMPLETE RESPONSE

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 14, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

We acknowledge receipt of the September 12, 2018 submission, which constituted a complete response to our December 19, 2017 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

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

Drug Product

1. We note that you have included elemental impurities in drug product specification. Please submit risk assessment and control of elemental impurities to demonstrate compliance with ICH Q3D. The information should include potential sources from raw materials, manufacturing equipment, container closure, water, etc.; identification of potential elemental impurities, and evaluation of the presence of elemental impurities in the drug product. The analytical methods should be able to detect potential elemental impurities and suitable for their intended purposes.

2. The Drug Master File (DMF [redacted (b) (4)] has been reviewed and found inadequate. The DMF holde [redacted (b) (4)] was notified of the deficiencies on April 10, 2019. Please consult with your DMF holder and provide the updated relevant P.4 sections. Do not respond to this ANDA Complete Response (CR) letter until you have confirmed that the DMF holder has responded to the DMF deficiency letter cited above or your amendment will not be considered a complete response.

3. In the September 26, 2017 submission, you established adhesive performance tests, i.e. (b) (4). You have included these tests in all stability time points. However, in the September 12, 2018 submission, we cannot locate the stability results for adhesive performance test for 3 batches made with MP1 line (Lots # L1304151, L1304191, and L1304201), and for 3 batches made with MP3 line (Lots # L1605301, L16053111, and L16053112) up to 6-month time point. To compare the adhesive performance results between batches made with MP1 line and MP3 line, provide all available adhesive performance test results on stability.

4. In your response to comment #9 of the September 12, 2018 CR amendment you state that you are requesting 24-month shelf life for the drug product. However, the current document in section 3.2.P.8.1 submitted on April 14, 2016 indicates that the currently proposed expiration dating for the marketing packaging is (b) (4) Clarify this discrepancy. In addition (b) (4)

PHARMACEUTICAL QUALITY/PHARMACOLOGY/TOXICOLOGY

The Pharmaceutical Quality/Pharmacology/Toxicology deficiencies have been classified as MAJOR because there is need for safety assessment of extractables and leachables as noted in Appendix A, Section A(2)(o) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required for establishing safety of the drug product. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources.

We completed Pharmacology/Toxicology review of your information submitted in support of safety of leachables and impurities in your proposed generic lidocaine patch (5%) (dated (b) (4) raise safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective. For TMS, you justified its general and dermal toxicity concerns using Cramer classification approach. Such an approach is not acceptable. For (b) (4) you did not address local toxicity concern for these compounds in the context of use of your proposed product, which has dermal route of administration and can be used chronically. Therefore, your safety assessment for these compounds is inadequate and not acceptable. To address these deficiencies, we recommend the following:

1. For TMS, address the systemic and local toxicity at its MDE level, fo (b) (4) address the local toxicity concern at their respective MDE levels from your proposed generic product. You may provide the justification information from published literature. The adequacy of the data from such a justification report will be a review issue upon submission.

2. Alternatively, you may conduct a 90-day repeated-dose toxicity study with your final, to-be marketed formulation to qualify the safety of the above listed compounds at their potential MDE levels. Consider an appropriate animal model, clinically relevant route of administration and context of use of your generic drug product in the design of the nonclinical studies. You may provide scientific rationale for the chosen animal model and the study design. In addition, the doses used for each compound in the repeated-dose toxicity study should provide adequate margins of safety for its proposed clinical exposure from your drug product. The adequacy of the data from such nonclinical studies will be a review issue upon submission. If you have clarifying questions on the design of the nonclinical studies, you may submit your study design via General Correspondence route to the Division of Clinical Review for our review.

DRUG SUBSTANCE/PROCESS/BIOPHARMACEUTICS/MICROBIOLOGY/FACILITY INSPECTION/ BIOEQUIVALENCE/CLINICAL BIOEQUIVALENCE/LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR320.24(a)), please continue to monitor for the availability of new and revised product specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling. It is also your responsibility to ensure that your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG PRODUCT/PHARMACOLOCY/TOXICOLOGY

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Andrew Potter, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9266.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

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

Denise
Toyer McKan

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ANDA 209190

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director Regulatory Affairs

Dear Sir:

This is in reference to your amendment received on September 12, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a standard major amendment. If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is May 11, 2019. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is July 11, 2019.

If you have any questions, contact Andrew Potter, Regulatory Project Manager, at (240) 402 - 9266.

Sincerely,

{See appended electronic signature page}

Andrew Potter
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Andrew Potter

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209190

COMPLETE RESPONSE

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 14, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

We acknowledge receipt of the September 26, 2017 submission, which constituted a complete response to our July 7, 2017 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Product

1. We acknowledge that you performed extractable studies (b) (4) in your submission dated September 26, 2017. Respond to the following:

    a. The first step in extractable studies is to identify possible extractables and identify expected potential impurities/extractables originating from the individual components of your drug product (including the printed backing film, release liner, and printed pouch). The source of the potential impurities/extractables includes chemical additives, monomers, oligomers, migrants, surface residues, or any chemical entities present in the drug product and packaging components. We recommend that you also contact the suppliers of your drug-product components to obtain information regarding any potential impurities. Provide a list of potential impurities/extractables and their component sources.

b. Selection of appropriate extraction media (usually three different solution/solvent systems, each having a distinct polarity) is critical to simulate a worst-case leachables profile during the extractable studies. Justify the solvent systems used for extraction given the possible pre-identified extractables (as described in part (a) of this deficiency). In addition, you have selected the extracting solvent (b) (4) of the formulation. Justify not using a range o (b) (4) ratios or other extraction solvents to cover the range of solvent polarities for which the pre-identified extractables are expected to have a high affinity and solubility. Also, provide information to support your assertion that the (b) (4) selected possesses similar polarity or hydrophobicity to the drug-product matrix.

c. We note that your LOQ is (b) (4) of the extract concentration. However, your analytical evaluation threshold (AET), as calculated on page 8 of 29 in report (b) (4), is inadequate. We acknowledge that you have used a safety concern threshold of (b) (4); however, have determined the safety concern threshold (SCT) for lidocaine patch to be (b) (4) per day for organic leachables. Therefore, we request you provide information on all compounds identified above AET using SCT o (b) (4) per day in the extractable studies you have performed. If the methods used do not have adequate detection at the corrected AET, revise your analytical methods or extraction procedure to achieve adequate sensitivity and repeat the extractables studies for each component. For any new extraction studies, clearly state the amount of solvent and components you used in the extraction process, as well as any calculations. Justify that your analytical methods are appropriate for detecting potential impurities/extractables that may have been extracted during your extractable studies.

d. We acknowledge that you used pouch material for your extractable study that had been previously used to package the drug product. Use of this material poses a risk to identifying all possible extractables. For example, compounds in the pouch may already have leached into the drug product during storage and therefore were not available for extraction. Provide extractable study results using virgin pouch material. In addition, confirm if you observe (b) (4) in the pouch material.

2. A leachable study is necessary to establish the safety of your drug product. For example, the presence o (b) (4) in the pouch of packaged drug product indicates that interaction between the drug product and pouch is likely during storage. Perform a leachable study on at least two batches of aged or expired final drug product to analyze potential leachables, including any extractables identified in extractables studies. Address the following:

a. The conditions of the leachable assessment should attempt to mimic as closely as possible “worst-case” clinical conditions of the skin (for example, during rigorous exercise, resulting in sweating) and the total leachable release should be measured over the entire labeled wear period. We recommend you use physiological fluid or biologically relevant solvent as extracting medium. Provide justification for the experimental conditions such as type of extracting medium, temperature, level of agitation, age of samples, etc., selected for the studies. The release liner should be removed from the system to adequately expose the adhesive layer to the biologically relevant solvent.

b. Provide assurance that your methods are capable of adequately detecting and monitoring the drug product for potential leachables, including elemental impurities.

c. Clarify the analytical evaluation threshold (AET) of the leachables in the drug product. Justify the AET using safety concern threshold (SCT) o [redacted] for organic leachables.

d. We have determined the safety concern threshold (SCT) for lidocaine patch to b [redacted] per day for organic impurities/leachables. A toxicological risk assessment should be provided for any organic leachable that exceed [redacted]. Any submitted safety assessment included in your response will be sent to the Office of Generic Drugs, Division of Clinical Review for Pharm/Tox review.

3. We note that you provide justification for variable values of lidocaine assay and release test obtained from MP1 line and MP3 lin [redacted] However, the dissolution results of the registration batches between 0-9 months [redacted] are [redacted] than the dissolution results of the registration batches after 12 month [redacted]). Justify the reason for the difference in dissolution results. Explain whether the change in dissolution method parameters, such as steel disc diameter, patch size, etc. resulted in th [redacted] in dissolution. Provide root cause of the change in dissolution results and justify that you have adequately performed dissolution on registration batches. In addition, the stability frequency per ICH Q1A(R2) should be every 3 months over the 1st year. Explain why you skipped the 3-month time point.

4. In your method validation [redacted], page 5 of 25, document date in 2014, you state that you will take the dissolution samples without dilution because the dilution makes the sample concentratio [redacted] than the validation range [redacted]. Respond to the following:

a. In the September 26, 2017 Complete Response Letter (CRL) #8b response, you corrected the dissolution results for lot L1605301 (made in May 2016) by using different dilution factor. You used dilution for dissolution sample preparation. Explain the discrepancy in the method about dilution. In addition, verify that the dissolution results for lot L1605301 is accurate. We note that the sample concentration with dilution is about [redacted] than the validation rang [redacted]

b. You changed the dissolution stability results for 3 registration batches at 12, 18, and 24-month time points in the September 26, 2017 submission. Explain the reason for the revision of the dissolution results for the 3 registration batches. Clarify which method you used to perform dissolution for lot L1605301, L16053111, and L16053112 and confirm that you obtained the accurate dissolution results.

5. Your September 26, 2017 CRL #15c response is inadequate. There are potential impurities in [redacted] that could be at leve [redacted] than the Threshold of Toxicological Concern (TTC) of [redacted] We request that you establish controls for adhesive impurities in the adhesive raw material or in the final drug product. Respond to the following deficiencies regarding the use of [redacted] (DMF [redacted]) in your proposed drug product:

   a. DMF# [redacted] has been reviewed and found inadequate. The DMF holde [redacted] was notified of the deficiencies on May 11, 2016. Do not respond to this ANDA CR letter until you have confirmed that the DMF holder has responded to the DMF CR letter cited above or your amendment will not be considered a complete response.

   b. Clarify the compound name for the [redacted] is, and for the unreacted monomer i [redacted] the limit of each monomer to be within the TTC, either in the adhesive raw material specifications or the drug product release specification. If you set the limit of a monomer impurity [redacted] than the TTC, provide pharm/tox data to support the safety of the monomer impurity at the maximum daily exposure (MDE). In case the same monomer impurity is present in bot [redacted] the amount considered for pharm/tox qualification should be combined amount from both adhesives to properly account for the MDE for the drug product.

   c. Provide the quantitative results and establish control of [redacted]

6. In the September 26, 2017 CRL #21 response, you explain that you use one patch for the pH test. Because pH is one of the critical quality attributes of the drug product, and you have not included the pH check in the in-process control during manufacture, using only one patch for the pH control to represent the pH of the whole batch is not adequate. Provide adequate control for pH of the drug product by using appropriate number of replicates, and revise the method accordingly.

7. Provide DMF references for release liner and pouch materials. Alternatively, provide information about the compositions, manufacture, and control of the raw materials for release liner and pouch materials.

8. Revise your stability table to include seal test in the stability data for lots L1605301, L16053111, and L16053112 in repor [redacted]. In addition, provide all available long-term stability data for lots L1605301, L16053111, and L16053112. We request that you update the stability tables with the revised stability specification.

9. The long-term stability results of all 3 registration batches at 36 months show the increasing trend in unknown impurity a (b) (4) This impurity increases from (b) (4) at release to (b) (4) at 36-month time point, reaching the specification limit o (b) (4). Discuss the increasing trend in the impurity a (b) (4)

10. In the September 26, 2017 CR# 40 response, you detected (b) (4) You state tha (b) (4) can be used as (b) (4) during the synthesis of lidocaine, and (b) (4) is an impurity of lidocaine. Discuss the levels o (b) (4) in the drug substance and the drug product, and provide appropriate control strategy. Clarify if you have observed (b) (4) on stability, and if (b) (4) is a degradant of lidocaine.

11. Pouch integrity is critical to drug product quality. We request you include vacuum test in your stability specification in post-approval stability protocol at every stability time point.

Drug Substance

(b) (4)

Device

The following deficiency has been identified while conducting the documentation review in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

(b) (4)

PROCESS/BIOPHARMACEUTICS/FACILITY INSPECTION/ BIOEQUIVALENCE/ CLINICAL BIOEQUIVALENCE/LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

Additionally, please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the *United States Pharmacopeia – National Formulary* (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

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.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as MAJOR.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/DEVICE

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

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

If you have any questions, call Andrew Potter, Regulatory Project Manager, Division of Project Management, at (240) 402-9266.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 12/19/2017 05:39:26PM
GUID: 5277df670008860f7e1231f730a8684c

ANDA 209190

AMENDMENT ACKNOWLEDGEMENT
Tier 1 Solicited
1st MINOR

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director Regulatory Affairs

Dear Sir:

We acknowledge receipt of your Tier 1 Solicited 1st MINOR amendment received for review on April 14, 2016, to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

This application is subject to the provisions of the Generic Drug User Fee Amendments of 2012 (GDUFA).

FDA has made an initial determination that the amendment submitted may be classified as a minor amendment. The GDUFA goal date for review of this ANDA is December 25, 2017. If FDA determines that an inspection is required to validate the information contained in this amendment, the GDUFA goal date for review of this ANDA will be July 25, 2018.

For more information, please refer to the guidance for industry, *ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA* available on FDA's website.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, contact Andrew Potter, Regulatory Project Manager, at (240) 402-9266.

Sincerely,

{See appended electronic signature page}

Andrew Potter
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

Andrew Potter

Digitally signed by Andrew Potter
Date: 9/29/2017 09:24:20AM
GUID: 53b5910400004b39a4f936d651797c40

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209190

COMPLETE RESPONSE

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 14, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

We acknowledge receipt of your amendments received on May 23, August 5, August 15, September 6, September 29, October 21, and December 9, 2016 and January 23, 2017.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

(b) (4)

[redacted]

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

(b) (4)

Biopharmaceutics

57. Submit the chromatograms generated for the specificity results of the drug release method validation (document number (b) (4)

58. Re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and report the linearity concentrations as percentage.

59. Provide an explanation for the (b) (4) in drug release at the 1440-minute (24-hour) time point.

60. Your proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:

    10 minutes: NMT (b) (4)%
    30 minutes: Between (b) (4)% - (b) (4)%
    120 minutes: NLT (b) (4)%

    We request that you acknowledge your acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

Microbiology

61. Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (reference: Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products - Questions and Answers).

Combination Product

62. You must demonstrate compliance with 21 CFR Part 4 before your application is considered approvable, therefore:

a. Please specify which firm has ultimate responsibility over the finished combination product. In addition, describe the organizational structure (i.e. organizational chart) and explain how it controls all levels of the product development and manufacturing (i.e. supplier agreements).

b. Please describe the design control system, which should include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Further, please provide a summary of the plan used to design the combination product.

c. Please summarize your procedure(s) for purchasing controls, including a description of the supplier evaluation process and the extent of control over suppliers. Also describe how it is ensured that products/services received are acceptable for their intended use and how changes made by subcontractors/suppliers will not affect the final combination product.

d. Please provide a description of your firm's corrective and preventive (CAPA) system, including how your CAPA system is integrated between the different facilities involved in the manufacturing of the combination product.

e. Please provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.

f. Please provide an explanation of how you will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. Additionally, please specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. Provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests, and the release of the finished combination product.

FACILITY INSPECTION/BIOEQUIVALENCE/CLINICAL BIOEQUIVALENCE/ LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrate bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstration bioequivalence, as required by FDA regulations (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

Additionally, please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the *United States Pharmacopeia – National Formulary* (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

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.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
1st MINOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/MICROBIOLOGY/ BIOPHARMACEUTICS

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, call Andrew Potter, Regulatory Project Manager, Division of Project Management, at (240) 402-9266.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 7/07/2017 01:21:41PM
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EASILY CORRECTABLE DEFICIENCY

ANDA 209190

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Rhodes Pharmaceuticals L.P. TEL: 401-262-9425

ATTN: Todd Delehant EMAIL: todd.delehant@pharma.com

FROM: Carol Lee FDA CONTACT EMAIL: Carol.Lee@fda.hhs.gov

Dear Dr. Delehant:

This communication is in reference to your abbreviated new drug application (ANDA) dated April 14, 2016, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within eleven (11) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 12410711

If you do not submit a complete response within eleven (11) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within eleven (11) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

LABELING:

1. GENERAL COMMENTS
   Include the country of origin on all your labeling pieces.

2. PATCH LABEL
   We note that final printed labeling (FPL) for the patch was not submitted for this application. Please ensure to include the established name and strength of the drug product, Lidocaine Patch 5%, on the patch when submitting FPL of the patch.

3. PATCH ENVELOPE
   a. Please ensure that the dotted line for cutting is only present on the top (as one single straight line), as opposed to along all four sides.
   b. We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Established Name) to improve its readability.
   c. Relocate "Rx Only" symbol and net quantity statement to the lower portion of principal display panel and remove the bold facetype.
   d. Revise "DOSAGE" to read as (b) (4)
   e. Add the following statement to appear in conjunction with the storage statement: "[see USP Controlled Room Temperature]".

4. CARTON LABELING
   See applicable patch envelope comments.

5. PRESCRIBING INFORMATION
   Please replace the abbreviations (b) (4) with "mcg" for clarity.

6. STRUCTURED PRODUCT LABELING (SPL)
   Revise the list of the inactive ingredients to reflect the list of the inactive ingredients in your package insert and consistent with your submission.

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

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Carol Lee, at Carol.Lee@fda.hhs.gov.

Sincerely,

Carol Lee, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 209190 November 18, 2016

EASILY CORRECTABLE DEFICIENCY
Original ANDA

RHODES PHARMACEUTICALS LP
498 WASHINGTON STREET
COVENTRY, RI 02816
USA

Attention: Mr. Todd M. Delehant, Ph.D., Director Regulatory Affairs

Dear Todd M. Delehant:

Please refer to your Abbreviated New Drug Application (ANDA) 209190, dated April 14, 2016 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The following Easily Correctable Deficiencies (ECD) regarding Study RP-LID-SSI have been identified:

Please refer to your ECD response dated 21 October 2016.

1. You have not provided the information we requested in Question 4.

    a. We wanted the data in a single dataset. You have submitted three datasets.

    b. We wanted the data for all patches of the same type (test or reference) for a subject in a single record (row). Your dataset has each patch in a separate record (row).

    c. The dataset FDA_Q4_1 has multiple records with inconsistent information. For example, Subject (b) (6) has two records with Test arm one at the lower application site and the other at the upper application site and two records with Reference arm again one at the lower application site and the other at the upper application site. This dataset seem to be inconsistent with the design and other datasets. Please make sure that your future submissions do not have such problems.

    d. There is no data definition file associated with the datasets. A data definition file is required for each dataset you submit.

    Please correct the deficiencies and submit the dataset and data definition file.

2. Your response to Question 2 shows that we have not understood the meaning of what time you referred to as the analysis time in ADAM datasets. This is caused by the lack of clear definition of the variables and what time is associated with it. Without a clear definition, it is normal to assume that if the parameter is "Patch Detached Prior to Assessment/Patch Removal?", the analysis time (adt) and analysis date and time (adtm) will provide the date and time of patch removal or detachment. Without proper and detailed

definition and explanation, especially for ADAM datasets, it is not possible to review your datasets and your application. For each ADAM dataset, please submit an explanation of each value of the variable "param" and what the associated values of the variables "aval", "avalc", "adt", "adtm" indicate.

3. Your response to Question 3 states "The protocol states that a subject was scheduled for a make-up patch application if either (i) patch adhesion assessed as <50% adhered but not detached (i.e., adhesion score of 3), or (ii) a scheduled visit was missed." However, we could not find the second condition in the protocol. Please provide the page number and the line number in the protocol where it is stated.

4. Your response to Question 3 states "Per protocol, no make-up patches were applied in response to patches with adhesion scores of 0, 1 or 2." However your datasets do not support this statement. For example, Subject (b) (6) had a maximum adhesion score of 1 for the reference patches 1 to 9 but adph.xpt has records for make-up reference patch for this subject. There are 34 such cases. Please clarify.

Please provide a complete response to these deficiencies by December 2, 2016. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
OFFICE OF BIOSTATISTICS/DBVIII
REFERENCE # 9446508

If FDA does not receive a complete response to these deficiencies by December 2, 2016 the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Vivianna Cowl, Project Manager at 301-796-0761.

Sincerely,

Vivianna Cowl
Office of Biostatistics
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

ANDA 209190 October 3, 2016

EASILY CORRECTABLE DEFICIENCY
Original ANDA

RHODES PHARMACEUTICALS LP
498 WASHINGTON STREET
COVENTRY, RI 02816
USA

Attention: Mr. Todd M. Delehant, Ph.D., Director Regulatory Affairs

Dear Todd M. Delehant:

Please refer to your Abbreviated New Drug Application (ANDA) 209190, dated April 14, 2016 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The following Easily Correctable Deficiencies (ECD) regarding Study RP-LID-SSI have been identified:

1. Please refer to your ECD response dated 15 August 2016. There are many discrepancies between the lists submitted and the datasets. Here are some examples:

   a. Subjec (b) (6) does not have a make-up patch in the adph.xpt dataset. However, makeup-patch-and-reason.pdf lists Subjec (b) (6) as having a make-up patch. There are many more such instances.

   b. Both test and reference Patch 1 were detached for Subjec (b) (6) according to adph.xpt dataset. However, these patches were not included in the list of detached patches in detached-patches-and-if-replaced.pdf.

   c. Subject (b) (6) did not have any detached patches according to adph.xpt. However, there were detached patches for this subject according to the list provided in detached-patches-and-if-replaced.pdf.

   Please explain these discrepancies.

2. There are discrepancies between submitted datasets. For example, the date and time of removal of test patch 5 for Subjec (b) (6) in adph.xpt i (b) (6) 2:00:00 PM and that in ex.xpt i (b) (6) 10:12:00 AM. There are 642 patches with such discrepancies. Please explain.

3. According to the protocol and the clinical study report for Study RP-LID-SSI, "If patch adhesion was assessed as <50% adhered but not detached (more than half the system lifting off of the skin without falling off), the subject was scheduled for a make-up patch application." However, according to the submitted data many

subjects had make-up patches even when the maximum adhesion score for the first 9 patches were 0, 1 or 2 (≥ 50% adhered) or 4 (complete detachment). Moreover, there were patches in the list of make-up patches in makeup-patch-and-reason.pdf (ECD response dated 15 August 2016) where make up patched were applied for complete detachments or for missing visits. There was no provision for make-up patches for completely detached or ≥ 50% adhered patches or for missed visits in the protocol and there was no mention of such cases in the clinical study report. Please explain.

4. Please provide a dataset per subject per treatment (patch type) with the following variables. All date and time should be numeric in SAS datetime format (not as character variables).

   - Subject id
   - Cohort
   - Treatment (patch type)
   - Application site
   - Whether it is in the per-protocol population for irritation (PPPI)
   - Reason for exclusion from PPPI
   - Whether it is in the per-protocol population for sensitization (PPPS)
   - Reason for exclusion from PPPS

For each of Patch 1 to Patch 9 and the make-up patch please include the following variables:

- Application date and time for Patch i
- Adhesion assessment date and time for Patch i
- Adhesion score for Patch i
- If Patch i is detached or removed
- Patch i detachment or removal date and time
- Whether actual or observed detachment time for Patch i (please see the explanation below*)
- Whether there was a replacement patch if Patch i was detached
- The application date and time for replacement patch for Patch i
- Detachment or removal date and time of replacement patch for Patch i

- Whether actual or observed detachment time for replacement patch for Patch i (please see the explanation below*)
- Adhesion score for replacement patch of Patch i
- Irritation assessment date and time for Patch i
- Dermal response score for Patch i
- Other effects score for Patch i
- Whether Patch i is moved to a new location from the previous patch location
- Dermal response score for the previous location if Patch i is moved to a new location
- Other effects score for the previous location if Patch i is moved to a new location

For the challenge phase:

- Patch application date and time for the challenge phase
- Adhesion score for the original patch in the challenge phase
- If the challenge phase patch is detached or removed
- Patch detachment or removal date and time in the challenge phase
- Whether actual or observed detachment time for original patch in the challenge phase (please see the explanation below*)
- Whether there was a replacement patch if challenge phase patch was detached
- The application date and time for replacement patch in the challenge phase
- Detachment or removal date and time of replacement patch in the challenge phase
- Whether actual or observed detachment time for replacement patch in the challenge phase (please see the explanation below*)
- Adhesion score for replacement patch in the challenge phase
- Sensitization assessment date and time for 30-minute post-removal assessment
- Dermal response score at 30-minute post-removal assessment
- Other effects score at 30-minute post-removal assessment

- Sensitization reaction at 30-minute post-removal assessment
- Sensitization assessment date and time for 24-hour post-removal assessment
- Dermal response score at 24-hour post-removal assessment
- Other effects score at 24-hour post-removal assessment
- Sensitization reaction at 24-hour post-removal assessment
- Sensitization assessment date and time for 48-hour post-removal assessment
- Dermal response score at 48-hour post-removal assessment
- Other effects score at 48-hour post-removal assessment
- Sensitization reaction at 48-hour post-removal assessment
- Sensitization assessment date and time for 72-hour post-removal assessment
- Dermal response score at 72-hour post-removal assessment
- Other effects score at 72-hour post-removal assessment
- Sensitization reaction at 72-hour post-removal assessment

*Explanation of actual and observed detachment time: If patch detachment time is noted exactly when it is detached it should be classified as actual detachment time. If a patch is observed to have already detached but the exact time when it was detached is not known, the time when it is observed should be classified as observed detachment time.

Please provide a complete response to these deficiencies by October 14, 2016. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
OFFICE OF BIOSTATISTICS/DBVIII
REFERENCE # 9446508

If FDA does not receive a complete response to these deficiencies by October 14, 2016 the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more

information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Vivianna Cowl, Project Manager at 301-796-0761.

Sincerely,

Vivianna Cowl
Office of Biostatistics
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209190 August 3, 2016

EASILY CORRECTABLE DEFICIENCY
Original ANDA

RHODES PHARMACEUTICALS LP
498 WASHINGTON STREET
COVENTRY, RI 02816
USA

Attention: Mr. Todd M. Delehant, Ph.D., Director Regulatory Affairs

Dear Todd M. Delehant:

Please refer to your Abbreviated New Drug Application (ANDA) 209190, dated April 13, 2016 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The following Easily Correctable Deficiencies (ECD) have been identified regarding Study RP-LID-SSI.

1. Please provide a list of subjects who skipped their scheduled visits along with the reason for skipping the visit.

2. Please provide a list of patches that were detached, the time when they were detached, whether a replacement patch was applied within 24 hours after detachment and the time when a replacement patch was applied.

3. Please provide a list of patches that were <50% adhered but not detached and if a make-up patch was applied for them.

4. Please provide a list of subjects who had a make-up patch and the reason for the make-up patch.

5. Subject (b) (6) had a missed visit but a make-up patch application. Please clarify the reason for the exclusion of their patches from the irritation analysis populations.

Please provide a complete response to these deficiencies by August 10, 2016. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
OFFICE OF BIOSTATISTICS/DBVIII
REFERENCE # 9433837

If FDA does not receive a complete response to these deficiencies by August 10, 2016 the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Vivianna Cowl, Project Manager at 301-796-0761.

Sincerely,

Vivianna Cowl
Office of Biostatistics
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Vivianna Cowl

Digitally signed by Vivianna Cowl
Date: 8/03/2016 02:07:24PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209190 August 2, 2016

EASILY CORRECTABLE DEFICIENCY
Original ANDA

RHODES PHARMACEUTICALS LP
498 WASHINGTON STREET
COVENTRY, RI 02816
USA

Attention: Mr. Todd M. Delehant, Ph.D., Director Regulatory Affairs

Dear Todd M. Delehant:

Please refer to your Abbreviated New Drug Application (ANDA) 209190, dated April 13, 2016 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

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1. Please provide a list of subjects who skipped their scheduled visits along with the reason for skipping the visit.

2. Please provide a list of patches that were detached, the time when they were detached, whether a replacement patch was applied within 24 hours after detachment and the time when a replacement patch was applied.

3. Please provide a list of patches that were <50% adhered but not detached and if a make-up patch was applied for them.

4. Please provide a list of subjects who had a make-up patch and the reason for the make-up patch.

5. Subject (b) (6) had a missed visit but a make-up patch application. Please clarify the reason for the exclusion of their patches from the irritation analysis populations.

Please provide a complete response to these deficiencies by August 8, 2016. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
OFFICE OF BIOSTATISTICS/DBVIII
REFERENCE # 9433837

If FDA does not receive a complete response to these deficiencies by August 8, 2016 the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Vivianna Cowl, Project Manager at 301-796-0761.

Sincerely,

Vivianna Cowl
Office of Biostatistics
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

To: todd.delehant@pharma.com
CC: Vivianna.cowl@fda.hhs.gov; Andrew.Potter@fda.hhs.gov; Sunny.Tse@fda.hhs.gov; Carol.Kim@fda.hhs.gov; teena.thomas@fda.hhs.gov; Fairouz.Makhlouf@fda.hhs.gov; Somesh.Chattopadhyay@fda.hhs.gov

Vivianna Cowl

Digitally signed by Vivianna Cowl
Date: 8/03/2016 12:41:38PM
GUID: 5565e5780007e8bf65dbef0657d63894

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209190

ACKNOWLEDGEMENT
ANDA RECEIPT

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.

Dear Todd M. Delehant:

We acknowledge receipt of your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

NAME OF DRUG: Lidocaine Patch, 5%

DATE OF APPLICATION: April 13, 2016

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: April 14, 2016

Reference is made to the Information Request dated May 16, 2016 and your response dated May 23, 2016.

This application is subject to the provisions of the Generic Drug User Fee Amendments of 2012 (GDUFA). The GDUFA goal date for review of this application is July 13, 2017. Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Scott Vehovic, Project Manager Team Leader, at Scott.Vehovic@FDA.HHS.GOV[1] or 240-402-3954.

Sincerely,

Ankit Ghodasara, Pharm.D.
Team Leader (Acting)
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Secure email between CDER and applicants may be useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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: 5/19/2016

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 209190

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 sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

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

Nicola M. Nicol -S

Digitally signed by Nicola M. Nicol -S
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: 2016.05.19 09:23:23 -04'00'