

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 62055/S-035

Name: Erythromycin Ethylsuccinate for Oral Suspension
USP, 200 mg/5 mL and 400 mg/5 mL

Sponsor: ANI Pharmaceuticals, Inc.

Approval Date: November 2, 2018

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APPLICATION NUMBER:
ANDA 62055/S-035

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-035

APPROVAL LETTER



ANDA 062055/S-035

**PRIOR APPROVAL SUPPLEMENT
APPROVAL - NEW STRENGTH**

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623
Attention: Ellen Camos
Vice President, Regulatory Affairs

Dear Madam:

This letter is in reference to your supplemental abbreviated new drug application (sANDA) received for review on May 25, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The sANDA, submitted as a "Prior Approval Supplement," provides for:

- Addition of new strength, Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL.
- Addition of Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL as a new therapeutic equivalent rating to Ery-Ped (Erythromycin Ethylsuccinate for Oral Suspension, USP), 200 mg/5 mL.

We have completed the review of this sANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the sANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Ery-Ped (Erythromycin Ethylsuccinate for Oral Suspension, USP), 200 mg/5 mL and 400 mg/5 mL, of Arbor Pharmaceuticals, LLC.

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 506l 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 506l(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 provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur

by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

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

CONTENT OF LABELING

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

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
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).



Priya
Shah

Digitally signed by Priya Shah
Date: 11/02/2018 10:23:46AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-035

LABELING

NDC 62559-630-01

**Erythromycin
Ethylsuccinate**
for Oral Suspension USP

**Erythromycin activity
200 mg per 5 mL**

when reconstituted



Rx only
100 mL
(when mixed)

Store granules, prior to mixing, below 86°F (30°C).

DIRECTIONS FOR PREPARATION: Slowly add 50 mL of water and shake vigorously to make 100 mL of suspension.

When prepared as directed, each 5 mL teaspoonful contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin in a cherry-flavored suspension.

Bottle contains erythromycin ethylsuccinate equivalent to 4 g erythromycin. Child-resistant closure not required; exemption approved by U.S. Consumer Product Safety Commission.

May be taken without regard to meals. Shake well before using. Oversize bottle provides shake space. Keep tightly closed.

Usual Dose: Children: 30 to 50 mg/kg/day in divided doses. See package insert for adult dose and full prescribing information.

10145 Rev 05/16

After mixing, store below 77°F (25°C) and use within 35 days.
Refrigeration not required.

Manufactured by:
ANI Pharmaceuticals, Inc.
Baudette, MN 56623



2"

4 1/4"

Label size: 2" x 4 1/4"

(b) (4)

NDC 62559-631-01

**Erythromycin
Ethylsuccinate**
for Oral Suspension USP

**Erythromycin activity
400 mg per 5 mL**

when reconstituted



Rx only
100 mL
(when mixed)

Store granules, prior to mixing, below 86°F (30°C).

DIRECTIONS FOR PREPARATION: Slowly add 50 mL of water and shake vigorously to make 100 mL of suspension.

When prepared as directed, each 5 mL teaspoonful contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin in a cherry-flavored suspension.

Bottle contains erythromycin ethylsuccinate equivalent to 8 g erythromycin. Child-resistant closure not required; exemption approved by U.S. Consumer Product Safety Commission.

May be taken without regard to meals. Shake well before using. Oversize bottle provides shake space. Keep tightly closed.

Usual Dose: Children: 30 to 50 mg/kg/day in divided doses. See package insert for adult dose and full prescribing information.

10145 Rev 05/16

After mixing, store below 77°F (25°C) and use within 35 days.
Refrigeration not required.

Manufactured by:
ANI Pharmaceuticals, Inc.
Baudette, MN 56623



2"

4 1/4"

Label size: 2" x 4 1/4"

(b) (4)

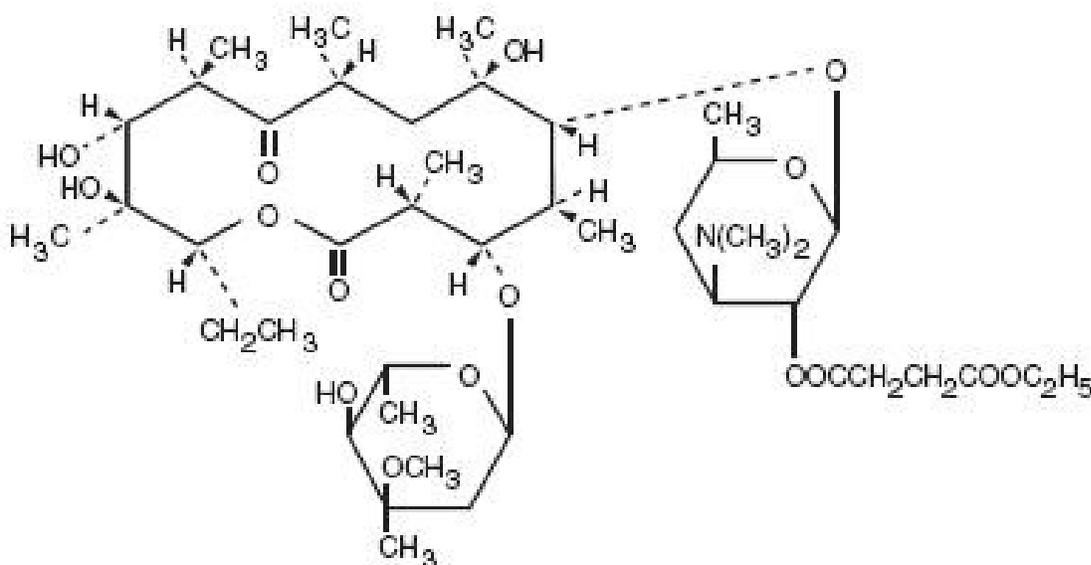
Erythromycin Ethylsuccinate for Oral Suspension USP

Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of erythromycin ethylsuccinate and other antibacterial drugs, erythromycin ethylsuccinate should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration. Erythromycin ethylsuccinate is known chemically as erythromycin 2'-(ethyl succinate). The molecular formula is $C_{43}H_{75}NO_{16}$ and the molecular weight is 862.06. The structural formula is:



Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 mL (teaspoonful) or 100 mg per 2.5 mL (dropperful) with an appealing cherry flavor. Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 mL (teaspoonful) with an appealing cherry flavor.

These products are intended primarily for pediatric use but can also be used in adults.

Inactive Ingredients

Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL contain the following inactive ingredients: lactose anhydrous, methylparaben, sodium citrate anhydrous,

povidone, simethicone, cherry flavor, polysorbate 80, and sucrose.

CLINICAL PHARMACOLOGY

Orally administered erythromycin ethylsuccinate suspension is readily and reliably absorbed under both fasting and nonfasting conditions.

Erythromycin diffuses readily into most body fluids. Only low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases in meningitis. In the presence of normal hepatic function, erythromycin is concentrated in the liver and excreted in the bile; the effect of hepatic dysfunction on excretion of erythromycin by the liver into the bile is not known. Less than 5 percent of the orally administered dose of erythromycin is excreted in active form in the urine.

Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk.

Microbiology:

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Many strains of *Haemophilus influenza* are resistant to erythromycin alone but are susceptible to erythromycin and sulfonamides used concomitantly.

Staphylococci resistant to erythromycin may emerge during a course of therapy.

Erythromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Gram-positive Organisms:

Corynebacterium diphtheriae

Corynebacterium minutissimum

Listeria monocytogenes

Staphylococcus aureus (resistant organisms may emerge during treatment)

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative Organisms:

Bordetella pertussis

Legionella pneumophila

Neisseria gonorrhoeae

Other Microorganisms:

Chlamydia trachomatis

Entamoeba histolytica

Mycoplasma pneumoniae
Treponema pallidum
Ureaplasma urealyticum

The following *in vitro* data are available.

Erythromycin exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 0.5 mcg/mL or less against most ($\geq 90\%$) strains of the following microorganisms; however, the safety and effectiveness of erythromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive Organisms:

Viridans group streptococci

Gram-negative Organisms:

Moraxella catarrhalis

Susceptibility Tests:

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of erythromycin ethylsuccinate and other antibacterial drugs, erythromycin ethylsuccinate should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Erythromycin ethylsuccinate for oral suspension USP is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae*, or *Haemophilus influenza* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower-respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes*.

Listeriosis caused by *Listeria monocytogenes*.

Pertussis (whooping cough) caused by *Bordetella pertussis*. Erythromycin is effective in

eliminating the organism from the nasopharynx of infected individuals rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Diphtheria: Infections due to *Corynebacterium diphtheriae*, as an adjunct to antitoxin, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma: In the treatment of infections due to *Corynebacterium minutissimum*.

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute Pelvic Inflammatory Disease Caused by *Neisseria gonorrhoeae*: As an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Syphilis Caused by *Treponema pallidum*: Erythromycin is an alternate choice of treatment for primary syphilis in penicillin-allergic patients. In primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Erythromycins are indicated for the treatment of the following infections caused by *Chlamydia trachomatis*: Conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to *Chlamydia trachomatis*.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Legionnaires' Disease caused by *Legionella pneumophila*. Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

Prophylaxis

Prevention of Initial Attacks of Rheumatic Fever

Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract, e.g., tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients.¹ The therapeutic dose should be administered for 10 days.

Prevention of Recurrent Attacks of Rheumatic Fever

Penicillin or sulfonamides are considered by the American Heart Association to be the drugs of choice in the prevention of recurrent attacks of rheumatic fever. In patients who are allergic to penicillin and sulfonamides, oral erythromycin is recommended by the American Heart Association in the long-term prophylaxis of Streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).¹

CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozone, or cisapride. (See **PRECAUTIONS - Drug Interactions**.)

Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

WARNINGS

Hepatotoxicity

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

QT Prolongation

Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Syphilis in Pregnancy

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration to prevent congenital syphilis. Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

***Clostridium difficile* Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including erythromycin ethylsuccinate, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Drug Interactions

Serious adverse reactions have been reported in patients taking erythromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension with calcium channel blockers metabolized by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) (see **PRECAUTIONS – Drug Interactions**).

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine. This interaction is potentially life-threatening, and may occur while using both drugs at their recommended doses (see **PRECAUTIONS – Drug Interactions**).

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels. (See package insert for lovastatin).

PRECAUTIONS

General

Prescribing erythromycin ethylsuccinate in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See **CLINICAL PHARMACOLOGY** and **WARNINGS** sections.)

Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome has been reported in patients receiving erythromycin therapy.

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical

pyloromyotomy. A possible dose-response effect was described with an absolute risk of IHPS of 5.1% for infants who took erythromycin for 8-14 days and 10% for infants who took erythromycin for 15-21 days.² Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed to contact their physician if vomiting or irritability with feeding occurs.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy. Observational studies in humans have reported cardiovascular malformations after exposure to drug products containing erythromycin during early pregnancy.

Information for Patients

Patients should be counseled that antibacterial drugs including erythromycin ethylsuccinate should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When erythromycin ethylsuccinate is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by erythromycin ethylsuccinate or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions

Theophylline: Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

There have been published reports suggesting that when oral erythromycin is given concurrently with theophylline there is a decrease in erythromycin serum concentrations of approximately 35%. The mechanism by which this interaction occurs is unknown. The decrease in erythromycin concentrations due to co-administration of theophylline could result in subtherapeutic concentrations of erythromycin.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with various oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. The following CYP3A based drug interactions have been observed with erythromycin products in post-marketing experience:

Ergotamine/dihydroergotamine: Post-marketing reports indicate that co-administration of erythromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of erythromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

Triazolobenzodiazepines: (such as triazolam and alprazolam) and *Related Benzodiazepines:* Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines.

HMG-CoA Reductase Inhibitors: Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Sildenafil (Viagra): Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. Reduction of sildenafil dosage should be considered. (See Viagra package insert.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, vinblastine, and bromocriptine.

Concomitant administration of erythromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. (See **CONTRAINDICATIONS**.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QTc interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed. (See **CONTRAINDICATIONS**.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin was co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes most likely due to the inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See **CONTRAINDICATIONS**.)

Colchicine: Colchicine is a substrate for both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Erythromycin is considered a moderate inhibitor of CYP3A4. A significant increase in colchicine plasma concentration is anticipated when co-administered with moderate CYP3A4 inhibitors such as erythromycin. If co-administration of colchicine and erythromycin is necessary, the starting dose of colchicine may need to be reduced, and the maximum colchicine dose should be lowered. Patients should be monitored for clinical symptoms of colchicine toxicity (see **WARNINGS**).

Drug/Laboratory Test Interactions

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dietary studies conducted with erythromycin stearate in rats up to 400 mg/kg/day and in mice up to 500 mg/kg/day (approximately 1-2 fold of the maximum human dose on a body surface area basis) did not provide evidence of tumorigenicity. Erythromycin stearate did not show genotoxic potential in the Ames, and mouse lymphoma assays or induce chromosomal aberrations in CHO cells. There was no apparent effect on male or female fertility in rats treated with erythromycin base by oral gavage at 700 mg/kg/day (approximately 3 times the maximum human dose on a body surface area basis).

Pregnancy

Teratogenic Effects. Pregnancy Category B:

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base by oral gavage at 350 mg/kg/day (approximately twice the maximum recommended human dose on a body surface area) prior to and during mating, during gestation, and through weaning. No evidence of teratogenicity or embryotoxicity was observed when erythromycin base was given by oral gavage to pregnant rats and mice at 700 mg/kg/day and to pregnant rabbits at 125 mg/kg/day (approximately 1-3 times the maximum recommended human dose).

Labor and Delivery

The effect of erythromycin on labor and delivery is unknown.

Nursing Mothers

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

Pediatric Use

See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.

Geriatric Use

Elderly patients, particularly those with reduced renal or hepatic function, may be at increased risk for developing erythromycin-induced hearing loss. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients. (See **WARNINGS**).

Elderly patients may experience increased effects of oral anticoagulant therapy while undergoing treatment with erythromycin. (See **PRECAUTIONS - Drug Interactions**).

Erythromycin ethylsuccinate for oral suspension 200 mg/5 mL contains 106.9 mg (4.6 mEq) of sodium per individual dose.

Erythromycin ethylsuccinate for oral suspension 400 mg/5 mL contains 106.9 mg (4.6 mEq) of sodium per individual dose.

Based on the 200 mg/5 mL strength, at the usual recommended doses, adult patients would receive a total of 855.2 mg/day (37.2 mEq) of sodium. Based on the 400 mg/5 mL strength, at the usual recommended doses, adult patients would receive a total of 427.6 mg/day (18.6 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

ADVERSE REACTIONS

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See **WARNINGS** section.)

Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes. (See **WARNINGS**.)

Allergic reactions ranging from urticaria to anaphylaxis have occurred. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely.

There have been reports of interstitial nephritis coincident with erythromycin use.

There have been rare reports of pancreatitis and convulsions.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

OVERDOSAGE

In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures should be instituted.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

Erythromycin ethylsuccinate oral suspensions may be administered without regard to meals.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. In mild to moderate infections, the usual dosage of erythromycin ethylsuccinate for children is 30 to 50 mg/kg/day in equally divided doses every 6 hours. For more severe infections this dosage may be doubled. If twice-a-day dosage is desired, one-half of the total daily dose may be given every 12 hours. Doses may also be given three times daily by administering one-third of the total daily dose every 8 hours.

The following dosage schedule is suggested for mild to moderate infections:

Body Weight	Total Daily Dose
Under 10 lbs	30-50 mg/kg/day 15-25 mg/lb/day
10 to 15 lbs	200 mg
16 to 25 lbs	400 mg
26 to 50 lbs	800 mg
51 to 100 lbs	1200 mg
over 100 lbs	1600 mg

Adults: 400 mg erythromycin ethylsuccinate every 6 hours is the usual dose. Dosage may be increased up to 4 g per day according to the severity of the infection. If twice-a-day dosage is desired, one-half of the total daily dose may be given every 12 hours. Doses may also be given three times daily by administering one-third of the total daily dose every 8 hours.

For adult dosage calculation, use a ratio of 400 mg of erythromycin activity as the ethylsuccinate to 250 mg of erythromycin activity as the stearate, base or estolate.

In the treatment of streptococcal infections, a therapeutic dosage of erythromycin ethylsuccinate should be administered for at least 10 days. In continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the usual dosage is 400 mg twice a day.

For treatment of urethritis due to *C. trachomatis* or *U. urealyticum*: 800 mg three times a day for 7 days.

For treatment of primary syphilis: Adults: 48 to 64 g given in divided doses over a period of 10 to 15 days.

For intestinal amebiasis: Adults: 400 mg four times daily for 10 to 14 days. Children: 30 to 50 mg/kg/day in divided doses for 10 to 14 days.

For use in pertussis: Although optimal dosage and duration have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.

For treatment of Legionnaires' Disease: Although optimal doses have not been established, doses utilized in reported clinical data were 1.6 to 4 g daily in divided doses.

HOW SUPPLIED

Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL is supplied in bottles of 100 mL (NDC 62559-630-01).

Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL is supplied in bottles of 100 mL (NDC 62559-631-01).

Recommended Storage:

Store Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL, prior to mixing, below 86°F (30°C). After reconstitution, Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL must be stored at or below 77°F (25°C) and used within 35 days; refrigeration is not required.

REFERENCES

1. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association: Prevention of Rheumatic Fever. *Circulation*. 78(4):1082-1086, October 1988.
2. Honein, M.A., et. al.: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *The Lancet* 1999;354 (9196): 2101-5.

Manufactured by:
ANI Pharmaceuticals, Inc.
Baudette, MN 56623



10147 Rev 05/18

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-035

LABELING REVIEWS

PRIOR APPROVAL SUPPLEMENT LABELING REVIEW

Division of Labeling Review
 Office of Regulatory Operations
 Office of Generic Drugs
 Center for Drug Evaluation and Research

Date of this Review	6/25/18
Review Cycle Number	1
ANDA(s) and Supplement Number(s)	062055/S-035
Applicant Name	ANI Pharmaceuticals, Inc.
Proprietary Name, Established Name, and Strength(s)	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 and 400 mg/5 mL
Current Received Date	5/25/18
Previous Received Date(s) of Proposed Supplement	None
Primary Labeling Reviewer	Manizheh Siahpoushan
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
- Acceptable for Filing Yes No NA

For labeling supplement(s):

N/A

For combined supplement(s):

The Division of Labeling Review has no comments. Labeling is acceptable.

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1. ANDA REGULATORY INFORMATION:

Type of Supplement: PAS - New Strength	
Are there any pending issues in DLR's SharePoint Drug Facts? If Yes, please explain:	NO
Is the drug product listed in the Policy Alert Tracker on DLRS SharePoint? If Yes, please explain:	
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm575163.htm	Yes, and applicant updated labeling referencing website.
Reason for Submission: Per the cover letter: ANI has performed the necessary requirements to add two new strengths to this ANDA: Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use) . Bioequivalence studies were executed per current FDA BE Guidance to demonstrate the equivalence of the proposed drug products to the reference listed drug (RLD); the RLD for this drug product is designated in the Orange Book to be EryPed® (Erythromycin Ethylsuccinate for Oral Suspension, USP), 400 mg/5 mL & 200 mg/ 5 mL under Arbor Pharmaceuticals' NDA 050207. The single RLD for this product family is NDA 050207 which contains the following products: E.E.S. Granules 200 mg/5 mL, EryPed® 200 mg/5 mL and EryPed 400 mg/5 mL. This ANDA was originally approved in November 1978 for a drug product strength equivalent to the E.E.S. Granules 200 mg/5 mL. This PAS provides for the addition of two drug product strengths (200 mg/5 mL and 400 mg/5 mL) that would be equivalent to the EryPed® product line.	
Is this supplement combined with another discipline?	YES
Is this product an OTC product?	NO
Is this ANDA the RLD?	NO

2. MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the Applicant and other review disciplines.

2.1.1 MATERIALS REVIEWED

Tables 1 and 2 provide a summary of recommendations for each material analyzed in this review.

Table 1: Review Summary of Container Label and Carton Labeling				
	Package Size	Draft or Final	Recommendation	Received Date
Container	100 mL	Final	Satisfactory	5/25/18
Blister	NA			
Carton	NA			
(Other - specify)	NA			
Table 2 Review Summary of Prescribing Information and Patient Labeling				

	Revision Date and/or Code	Draft or Final	Recommendation	Received Date
Prescribing Information	05/18	Draft	Satisfactory	5/25/18
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements	5/2018	NA	Satisfactory	5/25/18

2.1.2 MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 3.

Table 3: Review Model Labeling for Prescribing Information and Patient Labeling (Check all that apply)					
NDA/Original or Supplement:	050207/S-074	Approval Date:	4/23/18	Proprietary Name:	EryPed (erythromycin ethylsuccinate for oral suspension, USP)
Description of Original or Supplement:	<p>Please refer to your Supplemental New Drug Applications (sNDAs) dated and received February 23, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ERY-PED and E.E.S. (erythromycin ethylsuccinate) (NDA 050207), and PCE Tablets (erythromycin particles in tablets) (NDA 50611).</p> <p>These “Changes Being Effected” supplemental new drug applications revise the CONTRAINDICATIONS section as suggested in our January 29, 2018, correspondence. The following sentence was added:</p> <p>Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.</p>				
<input type="checkbox"/> BPCA TEMPLATE					
<input type="checkbox"/> OTHER (Describe)					
For OTC products Please provide PDP of NDA					

Reviewer Assessment:

Is the NDA listed in the discontinued section of the Orange Book? **NO**
 If yes, then comment below regarding the current model labeling.

Comment:

Note:

Both E.E.S and Ery-Ped are under the same NDA 050207.

S-073 approved on 8/17/2017 appears to be specific to E.E.S. only. Supplement provided for update to Microbiology section in the CLINICAL PHARMACOLOGY and corresponding REFERENCE section.

This Prior Approval supplemental new drug application proposes to update the **CLINICAL PHARMACOLOGY** and **REFERENCES** sections and **Microbiology** subsection of the labeling with changes made to the approved label for ANDA 61905 EES 400 (erythromycin ethylsuccinate). APPROVAL & LABELING

2.1.3 PATENTS AND EXCLUSIVITIES

Are there any remaining unexpired patents or marketing exclusivities for Model Labeling? **NO**

If YES go to the table 4 and assessments below.

Table 4 describes how the applicant certified to the [Orange Book](#) patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Table 4: Impact of Model Labeling Patents on ANDA Labeling					
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Labeling Impact ("Carve-out" or "None" or "Not addressed by firm")
N/A					

Table 5 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling				
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Labeling Impact ("Carve-out" or "None" or "Not addressed by firm")
N/A				

Reviewer Assessment:

Are there any recently expired patents or exclusivities? **NO**
 If yes, did these patents or exclusivities have any labeling impact? **N/A**

Comment: None.

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

The [USP](#) was searched on 6/25/2018.

Table 6: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES		Erythromycin Ethylsuccinate for Oral Suspension	Packaging and storage—Preserve in tight containers.
Pending Monograph Proposed	NO	NA	Same as above	No updates to the above

Reviewer Assessment:

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

Comment: None.

2.1.5 HISTORY OF ANDA

We evaluated previously approved and pending supplements (Table 7) to determine if actions are needed for the current review.

Table 7: Labeling History of ANDA

Original or Supplement	Approval Date	What post approval changes requested and were the changes addressed?
S-032	4/25/14	<p>Please make the following changes when and if you resume marketing of the product. PRESCRIBING INFORMATION/PHYSICIAN INSERT</p> <p>General</p> <p>i. We encourage the inclusion of "USP" in association with the established name of your drug product in the following places: the TITLE, DESCRIPTION, and INDICATIONS AND USAGE sections.</p> <p>ii. Please note that the established name of your drug product is "erythromycin ethylsuccinate for oral suspension." Please revise accordingly throughout the package insert.</p> <p>iii. Revise "µg" to "mcg."</p> <p>Applicant revised the labeling as requested.</p>
<p align="center">Are there any Pending Labeling Supplements for this ANDA that impact labeling? YES</p>		

Table 7: Labeling History of ANDA

Supplement	Submission Date	Labeling Impact
S-034	12/16/16	<p data-bbox="1003 260 1049 281">(b) (4)</p> <p data-bbox="415 317 740 348">This supplement provides for:¹</p> <ul data-bbox="456 380 1422 436" style="list-style-type: none"> <li data-bbox="456 380 1422 436">• A new manufacturing and testing facility, ANI Pharmaceuticals Inc., located in Baudette, MN; <div data-bbox="440 436 1446 590" style="background-color: #cccccc; height: 73px; margin: 5px 0;"> <p data-bbox="1403 432 1448 453">(b) (4)</p> </div> <p data-bbox="889 590 935 611">(b) (4)</p> <p data-bbox="415 667 472 699">S-034</p> <p data-bbox="415 709 1349 741">This Prior Approval Supplement is proposing a new manufacturing, packaging, and testing facility.</p> <p data-bbox="415 747 1511 863">Labeling review C3 for S-034 was based on the 2/14/18 submission to provide for updated labeling to align with the current labeling from the RLD, NDA 050207-S073, approved August 17, 2017. The container labels were revised to incorporate minor editorial changes and to modify the layout and dimensions. completed on 3/2/18 was adequate.</p> <div data-bbox="407 863 1533 1472" style="background-color: #cccccc; height: 290px; margin: 5px 0;"> <p data-bbox="1490 858 1536 879">(b) (4)</p> </div>

3. ASSESSMENT OF CURRENT SUPPLEMENT'S LABELING

3.1.1 CONTAINER AND CARTON LABELS

Reviewer Assessment:

Were container or carton labels submitted in this supplement? **YES**

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

Comment: Acceptable.

Approved/discontinued label from AR-27 dated 1/25/17 (based on NDA 050207 E.E.S.):

(b) (4)

The side by side comparison provided by the applicant (only one strength is shown):

Top Label (ANI Pharmaceuticals, Inc.):

- 1: NDC 62559-630-01
- 2: Erythromycin Ethylsuccinate for Oral Suspension USP
- 3: Erythromycin activity 200 mg per 5 mL when reconstituted
- 4: DIRECTIONS FOR PREPARATION: Slowly add 50 mL of water and shake vigorously to make 100 mL of suspension.
- 5: Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623
- 6: Barcode
- 7: Rx only 100 mL (when mixed)
- 8: Usual Dose: Children: 30 to 50 mg/kg/day in divided doses. See package insert for adult dose and full prescribing information.
- 9: 10145 Rev 05/16
- 10: After mixing, store below 77°F (25°C) and use within 35 days. Refrigeration not required.

Bottom Label (Arbor Pharmaceuticals, Inc.):

- 1: NDC 24338-132-13
- 2: EryPed® 200
- 3: ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP
- 4: Erythromycin activity 200 mg per 5 mL when reconstituted
- 5: DIRECTIONS FOR MIXING: Add 50 mL water and shake vigorously. This makes 100 mL of suspension. For best taste mix at least 15 to 20 minutes before dosing.
- 6: Contains erythromycin ethylsuccinate equivalent to 4 g erythromycin.
- 7: Rx only
- 8: Usual dose: Children: 30-50 mg/kg/day in divided doses. See enclosure for adult dose and full prescribing information.
- 9: Exp. Lot 04-A-8998-R1 (Lot 6 302)
- 10: Before mixing, store below 80°F (30°C).

TABLE OF ANNOTATIONS – 200 mg per 5 mL LABEL

ANNOTATION	PROPOSED (ANI Pharmaceuticals, Inc.)	RLD
1. Product name updated to reflect generic product.	Erythromycin Ethylsuccinate for Oral Suspension USP	EryPed® 200 ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP
2. National Drug Code (NDC) updated to reflect ANI product.	NDC 62559-630-01	NDC 24338-132-13
3. Manufacturer's Logo changed to reflect ANI.		
4. Storage statement modified to clearly indicate is applicable to the granules.	Store granules, prior to mixing, below 86°F (30°C).	Before mixing, store below 86°F (30°C).
5. Preparation instructions modified to reflect ANI product formulation. Taste statement was removed as it is specific to the RLD flavoring agent.	DIRECTIONS FOR PREPARATION: Slowly add 50 mL of water and shake vigorously to make 100 mL of suspension.	DIRECTIONS FOR MIXING: Add 53 mL water and shake vigorously. This makes 100 mL of suspension. For best taste mix at least 15 to 20 minutes before dosing.
6. Active amount statement modified for consistency with ANI products and to reflect ANI flavor.	When prepared as directed, each 5 mL teaspoonful contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin in a cherry-flavored suspension.	When mixed as directed, each teaspoonful (5 mL) contains: Erythromycin ethylsuccinate equivalent to erythromycin200 mg in a fruit-flavored, (b) (4)
7. Manufacturer/Distributor information updated to reflect ANI.	Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623	Arbor Pharmaceuticals, Inc. Atlanta, GA 30328
8. Food statements moved to side panel and combined.	May be taken without regard to meals.	May be taken before, after, or with meals. DOSAGE MAY BE ADMINISTERED WITHOUT REGARD TO MEALS.
9. Label Control Number updated to reflect ANI.	10145 Rev 05/18	04-A898-R1 (List 6302)
10. Contents statement updated for consistency with ANI products.	100 mL (when mixed)	100 mL For Oral Suspension (when mixed)

Reviewer's Assessment:

With regards to the statement, "Store granules, prior to mixing...", the use of the words "granules" is acceptable based on the finished drug product specification from 3.2.P.5:

(b) (4)

The difference in the quantity of water to be added before mixing (i.e., 50 mL), the quantity is specific to the ANDA drug product.

The other differences are consistent with the applicant's other approvable container label under S-034 (refer to Table 7) for the other formulation.

3.1.2 MODEL CONTAINER LABELS

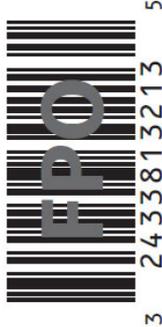
Provide the reference listed drug labels if applicant submits container, blister, carton, etc.

Model container/carton/blister labels [Source: NDA 50207 AR-25, submitted 5/31/2013]

Exp.
Lot

04-A898R1 (List 6302)

May be taken before, after or with meals.
Shake well before using. Oversize bottle provides shake space. Keep tightly closed.
Refrigeration not required.
Store below 77°F (25°C) and use within 35 days.



3 2433813213 5

NDC 24338-132-13
100 mL For Oral Suspension
(when mixed)

EryPed® 200

ERYTHROMYCIN
ETHYLSUCCINATE FOR
ORAL SUSPENSION, USP
Erythromycin activity
200 mg per 5 mL
when reconstituted

Rx only



Before mixing, store below 86°F (30°C).
DIRECTIONS FOR MIXING: Add 53 mL water and shake vigorously. This makes 100 mL of suspension. For best taste mix at least 15 to 20 minutes before dosing. Contains erythromycin ethylsuccinate equivalent to 4 g erythromycin.
Child-resistant closure not required; exemption approved by U.S. Consumer Product Safety Commission.
When mixed as directed, each teaspoonful (5 mL) contains:
Erythromycin ethylsuccinate equivalent to erythromycin.....200 mg in a fruit-flavored, aqueous vehicle.
DOSAGE MAY BE ADMINISTERED WITHOUT REGARD TO MEALS.
Usual dose: Children: 30-50 mg/kg/day in divided doses. See enclosure for adult dose and full prescribing information.

Arbor Pharmaceuticals, Inc.
Atlanta, GA 30328

Exp.
Lot

04-A899-R1 (List 6305)

May be taken before, after or with meals.
Shake well before using. Oversize bottle provides shake space. Keep tightly closed.
Refrigeration not required. After mixing, store below 77°F (25°C) and use within 35 days.



3 2433813013 1

NDC 24338-130-13
100 mL For Oral Suspension
(when mixed)

EryPed® 400

ERYTHROMYCIN
ETHYLSUCCINATE FOR
ORAL SUSPENSION, USP
Erythromycin activity
400 mg per 5 mL
when reconstituted

Rx only



Before mixing, store below 86°F (30°C).
DIRECTIONS FOR MIXING: Add 49 mL water and shake vigorously. This makes 100 mL of suspension. Contains erythromycin ethylsuccinate equivalent to 8 g erythromycin. When mixed as directed, each teaspoonful (5 mL) contains: Erythromycin ethylsuccinate equivalent to erythromycin.....400 mg in a banana-flavored, aqueous vehicle.
DOSAGE MAY BE ADMINISTERED WITHOUT REGARD TO MEALS.
Usual dose: Children: 30-50 mg/kg/day in divided doses. See package enclosure for full prescribing information.
Child-resistant closure not required; exemption approved by U.S. Consumer Product Safety Commission.

Arbor Pharmaceuticals, Inc.
Atlanta, GA 30328

3.1.3 RX PRESCRIBING INFORMATION AND PATIENT LABELING

Reviewer Assessment:

Was labeling submitted in this supplement? **YES**

Are the labeling contained in the submission the same as the review model labeling (not including allowable differences under 21 CFR 314.94(a)(8))? **YES**

Is the Prescribing Information shared by other ANDAs? **NO** (If yes please list ANDA numbers).

Comment: Acceptable.

As per the Guidance for Industry titled, “Systemic Antibacterial and Antifungal Drugs: Susceptibility Test Interpretive Criteria Labeling for NDAs and ANDAs”, the applicant deleted the following sections from the labeling:

(b) (4)



...and added the following text at the end of the CLINICAL PHARMACOLOGY/Microbiology subsection:

Susceptibility Tests:

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

3.1.4 INACTIVE INGREDIENTS CHANGE

Are there changes to the inactives in the Rx DESCRIPTION section or OTC labeling? **NO** (If NO, go to section 3.1.5.)

Table 8: Comparison of Inactive Ingredients Contained in Model Labeling and ANDA Labeling		
Model Labeling	Approved ANDA Labeling	Proposed ANDA Labeling
Ery-Ped 200, Ery-Ped 400: Caramel, polysorbate, sodium citrate, sucrose, xanthan gum and artificial flavors.	artificial cherry flavor, lactose anhydrous, methylparaben, polysorbate 80, povidone, simethicone, sodium citrate anhydrous, and sucrose.	lactose anhydrous, methylparaben, sodium citrate anhydrous, povidone, simethicone, cherry flavor, polysorbate 80, and sucrose

Reviewer Assessment:

Are the inactive ingredients in the labeling consistent with the Composition Statement in Module 3.2.P.1 of the submission? **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**

Comment: Acceptable, pending quality assessment.

Module 3.2.P.1

Table 2 Final Reconstituted Formulation for EES for OS (35 Day) 200 mg/5 mL and 400 mg/5 mL

Component	Function	400 mg/5 mL		200 mg/5 mL	
		% w/v	mg/dose	% w/v	mg/dose
Erythromycin Ethylsuccinate USP	Drug Substance				(b) (4)
Lactose NF (Anhydrous) (b) (4)					
Methylparaben NF					
Sodium Citrate Anhydrous USP					
Povidone USP (b) (4)					
Simethicone USP					
(b) (4) Cherry Flavor, (b) (4)					
Polysorbate 80 NF					
Sucrose NF (b) (4)					

(b) (4)

8. Sodium Content Calculation

The proposed Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use) drug product is an antibiotic; therefore, the calculation of sodium per unit-dose is provided. The

(b) (4)

Conclusion:

EES 200 and 400 (35 Day In-Use) products each contain 106.9 mg (4.6 mEq) of sodium per individual dose.

Based on the 200 mg/5 mL strength, at the usual recommended doses, adult patients would receive a total of 855.2 mg/day (37.2 mEq) of sodium.

Based on the 400 mg/5 mL strength, at the usual recommended doses, adult patients would receive a total of 427.6 mg/day (18.6 mEq) of sodium.

The above conclusion is consistent with the following labeling claim under PRECAUTIONS/Geriatric Use:

Erythromycin ethylsuccinate for oral suspension 200 mg/5 mL contains 106.9 mg (4.6 mEq) of sodium per individual dose.

Erythromycin ethylsuccinate for oral suspension 400 mg/5 mL contains 106.9 mg (4.6 mEq) of sodium per individual dose.

Based on the 200 mg/5 mL strength, at the usual recommended doses, adult patients would receive a total of 855.2 mg/day (37.2 mEq) of sodium. Based on the 400 mg/5 mL strength, at the usual recommended doses, adult patients would receive a total of 427.6 mg/day (18.6 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

3.1.5 HOW SUPPLIED CHANGE

Are there changes to the dosage form description(s) or package size(s) in the Rx HOW SUPPLIED section or OTC package sizes? **YES** (If NO, go to section 3.1.6.)

Table 9: Comparison of Dosage Form Description(s) and Package Size(s) Contained in Model Labeling and ANDA Labeling

<p>Model Labeling</p>	<p>NDA 050207, Ery-Ped labeling: Ery-Ped 200 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 100 mL (NDC 24338-132-13) Ery-Ped 400 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 100 mL (NDC 24338-130-13) Recommended Storage: Store Ery-Ped 200 and Ery-Ped 400, prior to mixing, below 86°F (30°C). After reconstitution, Ery-Ped 200 and Ery-Ped 400 must be stored at or below 77°F (25°C) and used within 35 days; refrigeration is not required.</p> <p>NDA 050207, EES labeling: GRANULES 200 mg per 5 mL (erythromycin ethylsuccinate for oral suspension, USP) are pink granules with a cherry aroma and are supplied in 100-mL (NDC 24338-134-02) and 200-mL (NDC 24338-136-10) size bottles. Following reconstitution E.E.S. Granules become a pink opaque suspension with a cherry aroma. E.E.S. 400 film-coated tablets (erythromycin ethylsuccinate tablets, USP) 400 mg, are supplied as pink oval tablets imprinted with the two letter designation, EE, in bottles of 100 (NDC 24338100-13). Recommended Storage Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Store granules, prior to mixing, at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. After mixing, refrigerate and use within 10 days.</p>
<p>Approved ANDA Labeling</p>	<p>Note that the previously approved ANDA product was based on NDA 050207, E.E.S. (grayed out, above)</p> <p>Erythromycin Ethylsuccinate for Oral Suspension USP is available as: 200mg/5mL: Each 5 mL teaspoon of reconstituted cherry-flavored suspension contains activity equivalent to 200 mg of erythromycin. Available in bottles of: 100 mL NDC 62559-440-01 200 mL NDC 62559-440-02 Recommended storage Store granules, prior to mixing, below 86°F (30°C). After mixing, refrigerate and use within ten days.</p>
<p>Proposed ANDA Labeling</p>	<p>Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL is supplied in bottles of 100 mL (NDC 62559-630-01). Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL is supplied in bottles of 100 mL (NDC 62559-631-01). Recommended Storage: Store Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL, prior to mixing, below 86°F (30°C). After reconstitution, Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL must be stored at or below 77°F (25°C) and used within 35 days; refrigeration is not required.</p>

Reviewer Assessment:

Are there changes to the dosage form description(s) or package size(s) in the Rx HOW SUPPLIED section or OTC package sizes? **YES**

Are the changes to the dosage form descriptions in the HOW SUPPLIED section consistent with the Drug Product Specifications in Module 3.2.P.5.1 of the submission? **YES**

Are all of the submitted labels and labeling reflected in the HOW SUPPLIED section? **YES**

Does the ANDA require the same color coding as the Model Labeling? **NA**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**

Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**

Is the storage or dispensing statement acceptable **YES**

Comment: Acceptable, pending quality assessment.

3.1.6 CONTAINER/CLOSURE

Were container and closure information submitted? **YES** (If NO, go to section 3.1.7.)

Reviewer Assessment:

Are the changes to the package size(s) supported by the container/closure information in Module 3.2.P.7 of the submission? **YES**

Describe the container closure (e.g., 30s CRC, 100s non-CRC) in the **Comment** 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](#), [Ophthalmic](#) and [Controlled Substances](#) **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 <7> Labeling? **NA**

What is the cap color? [Click here to enter text.](#)

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

Comment: Acceptable, pending quality assessment.

Module 3.2.P.7:

ANI proposes the following container closure system for the Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL (35 Day In-Use).

(b) (4)



3.1.7 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES** (If NO, go to section 3.1.8.)

Table 10: 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: e.g., Chemistry Review, Product Specification in 3.2.P.5.1 and Commercial Batch Record in 3.2.P.3.3)
Click here to enter text	Click here to enter text	Click here to enter text

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**

Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Comment: Acceptable.

3.1.8 MANUFACTURING/DISTRIBUTING STATEMENT COMPARISON

Reviewer Assessment:

Are there changes to the manufacturing/distributing statements? **NO**

Table 10: Manufactured by Statement		
Previously Approved	Currently Proposed	Assessment
Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623	Manufactured by: ANI Pharmaceuticals, Inc. Baudette, MN 56623 10147 Rev 05/18	Acceptable.

Module 3.2.P.3:

DRUG PRODUCT				
Name	Address	Contact	Facility ID No.	Function/ Responsibility
ANI Pharmaceuticals, Inc.	210 Main Street West Baudette, MN 56623	David J. Sullivan, Ph.D. VP, Quality Operations Phone: 218.634.3507 Fax: 218.634.3540 Email: david.sullivan@anipharmaceuticals. com	FEI: 2111358	Drug Substance: Analytical Testing Drug Product: Manufacturing, Packaging, Labeling, In-Process Analytical Testing, Final Dosage Form Release Analytical Testing, Stability Analytical Testing Excipients: Analytical Testing, Microbiological Testing
			DUNs: 148515737	

4. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Comments: None.

5. SPECIAL CONSIDERATIONS

Include other information that may pertain to your drug product application.

Comment: None.



Manizheh
Siahpoushan

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Date: 6/26/2018 04:12:39PM
GUID: 50814c7000007a4f0582207115192fdf



Theresa
Liu

Digitally signed by Theresa Liu
Date: 6/29/2018 10:11:19AM
GUID: 508da70a00028d58911de18a598cda6f

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-035

CHEMISTRY REVIEWS

CHECKLIST FOR THE CHEMISTRY REVIEW:

ANDA 062055/S-035

Function	Performed By (Initial and Date)	Check appropriate box
Is this package for new strength PAS?	RBPM YT 10/26/18	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
DMF adequate? (b) (4)	RBPM YT 10/26/18	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No *(see comments)
Any outstanding consults?	RBPM YT 10/26/18	<input type="checkbox"/> Yes *(see comments) <input checked="" type="checkbox"/> No
Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee PS 10/26/18	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Are all facility inspections acceptable?	RBPM YT 10/26/18	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Is microbiology recommendation adequate for sterile products?	RBPM YT 10/26/18	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee PS 10/26/18	<input type="checkbox"/> Yes How many: _____ <input checked="" type="checkbox"/> No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee PS 10/26/18	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No *(see comments) <input type="checkbox"/> N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee PS 10/26/18	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No *(see comments) <input type="checkbox"/> N/A
Is the final review uploaded into the current IT platform?	RBPM YT 10/26/18	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Comments		
Division	Name	Date



Paul
Schwartz

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Discipline reviews and Facilities:

(Record the status of discipline reviews and facilities as NA {Not applicable}, AC {Acceptable}, PN {Pending})

DISCIPLINES INVOLVED	REVIEW OUTCOME	DISCIPLINES INVOLVED	REVIEW OUTCOME
Chemistry	AC	Bioequivalence	AC
		Biopharmaceutics	AC
Microbiology	NA	Facilities	AC
Labeling	AC	DMF	Adequate
SUBMISSIONS REVIEWED			
Submission Date (from Cover Letter):	May 25, 2018		
Amendment(s) Date (from Amendment Cover Letter):	June 4, 2018; June 14, 2018; June 19, 2018; September 27, 2018		

PAS ASSESSMENT FORM

ANDA No./Supplement No.: 62055/S35

Name of applicant and address (from 356h): ANI Pharmaceuticals, Inc.
210 Main Street West, Baudette
MN 56623

Drug Product Name, Dosage Form and Strength(s): Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL & 200 mg/5 mL.

Reporting Category: PAS

Supplement provides for: Addition of 2 new strengths to the Drug product Erythromycin Ethylsuccinate for Oral Suspension USP, i.e., 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use).

Relevant supporting DMFs cited and/or reviewed (if any), name and location of DMF Holder(s), and DMF status: Erythromycin Ethylsuccinate USP, DMF # (b) (4) Type II DMF, held by (b) (4) (b) (4) the DMF has been reviewed up-to-date by L. Mu on October 19, 2018 and was found to be Adequate.

Assessment Notes: The firm proposes to add two new strengths to this ANDA: Erythromycin Ethylsuccinate for Oral Suspension USP, **200 mg/5 mL (35 Day In-Use)** and **400 mg/5 mL (35 Day In-Use)**. The RLD for this drug product in the Orange Book is EryPed® (Erythromycin Ethylsuccinate for Oral Suspension, USP), 400 mg/5 mL & 200 mg/ 5 mL under Arbor Pharmaceuticals' NDA 050207.

Note that NDA 050207 contains the following products: E.E.S. Granules 200 mg/5 mL, EryPed® 200 mg/5 mL and EryPed 400 mg/5 mL. When ANDA# 62055 was originally approved in November 1978, the drug product strength is equivalent to the E.E.S. Granules 200 mg/5 mL (10 Day in-use).

This supplement was Accept for Filing on June 20, 2018.

Data in support of the supplement are found satisfactory (record Yes or No): Yes

Deficiencies noted (list deficiencies or record None): None

Recommendation (mark X for one):

This supplement is recommended for approval.

This supplement is recommended for approval pending acceptable discipline review(s).

This supplement is **NOT** recommended for approval, deficiencies noted above.

Reviewer's Name Huiqi He

Date: October 22, 2018

QAL's Name Kathy Woodland Outlook



Huiqi
He

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Kathy
Woodland Outlaw

Digitally signed by Kathy Woodland Outlaw
Date: 10/24/2018 09:14:49AM
GUID: 508da70000028671b774f642ccb12211

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-035

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	062055-SUPP-035		
Drug Product Name	Erythronycin Ethylsuccinate for Oral Suspension USP		
Strength(s)	Eq 200 mg base/5 mL (35 Day In-Use) and Eq 400 mg base/5 mL (35 Day In-Use) ¹		
Applicant Name	ANI Pharmaceuticals, Inc.		
Applicant Address	210 Main Street West, Baudette, MN 56623, USA		
US Contact Name and US Mailing Address	Ellen Camos, Vice President of Regulatory Affairs 210 Main Street West, Baudette, MN 56623, USA Email: ellen.camos@anipharmaceuticals.com		
US Contact Telephone Number	(b) (6)		
US Contact Fax Number	888.519.0459		
Original Submission Date(s)	07/28/1997		
Submission Date(s) of Amendment(s) Under Review	05/25/2018 (Supplement-035, SD-95)		
Primary Reviewer	Yibo Wang, Ph.D.		
Secondary Reviewer	Jennifer N. Miller, Ph.D.		
Tertiary Reviewer	N/A		
Study Number(s)	739/17	740/17	
Study Type(s)	Fasting	Fed	
Strength(s)	400 mg/5 mL	400 mg/5 mL	
Clinical Site	QPS Bioserve India Pvt. Limited		
Clinical Site Address	#6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India. Tel: +91-40-4377 0873 / 1875; Fax +91-40-4377 0877		
Analytical Site	(b) (4)		
Analytical Site Address			
OSIS status	<u>Backlog, Year 1 and Year 2 ANDAs</u> <input type="checkbox"/> Pending <input type="checkbox"/> Complete		<u>Post October 1, 2014 ANDAs</u> <input type="checkbox"/> To Be Determined by OSIS <input type="checkbox"/> Pending For Cause Inspection <input checked="" type="checkbox"/> Complete

¹ For the ease of review, "Eq X mg base/5 mL" will be referred as to "X mg/5 mL".

	<input type="checkbox"/> N/A (Waiver/Deem Bioequivalent) ²		<input type="checkbox"/> N/A (Waiver/Deem Bioequivalent) ² Error! Bookmark not defined.
Waiver	<input checked="" type="checkbox"/> Granted <input type="checkbox"/> Tentatively granted <input type="checkbox"/> Not granted <input type="checkbox"/> N/A		
QC Dissolution	<input type="checkbox"/> Pending <input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate		
Formulation	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate		
Will Response to CR Result in a Reformulation?	<input type="checkbox"/> Possibly <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A		
Deficiency Classification	<input type="checkbox"/> Major <input type="checkbox"/> Minor/IR <input checked="" type="checkbox"/> N/A (Review is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate		
Product Specific Guidance (PSG) Referenced in Review	<p><i>Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)</i></p> <input checked="" type="checkbox"/> Recommended/Latest Revision Date: <u>Recommended Jun 2016</u> RLD Number: <u>NDA_050257</u> <input type="checkbox"/> N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
95, 98, 99	Fasting	400 mg/5 mL	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate
95, 98, 99	Fed	400 mg/5 mL	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate
95, 98, 99	Waiver	200 mg/5 mL	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate

1 EXECUTIVE SUMMARY

This is a review of a **Prior Approval Supplement (PAS)**.

On May 25, 2018, the applicant submitted supplement-035 as a PAS. This submission is to add two new strengths to ANDA 062055: Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL (35 Days In-Use) and 400 mg/5 mL (35 Days In-Use).

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

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, ANI Pharmaceuticals, Inc.'s Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL, to the corresponding strength of the RLD product, Arbor Pharmaceuticals LLC's EryPed® (erythromycin ethylsuccinate) Oral Granules, 400 mg/5 mL. Each of the BE studies was designed as a single-dose, two-treatment, three-period, three-sequence, crossover, partial replicate study in healthy male subjects. The applicant's fasting and fed BE studies are acceptable. The results are summarized in the tables below.

Erythromycin Ethylsuccinate for Oral Suspension USP, 1 x 400 mg/5 mL Fasting Bioequivalence Study No. 739/17, N=58 (Male=58 and Female=0) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Unscaled								
Parameter (ng)		Test	RLD	Ratio	90% C.I.			
AUC _{0-t} (hr *ng/ml)		6222.35	6024.11	1.03	94.78	112.56		
AUC _∞ (hr *ng/ml)		6752.84	6562.01	1.03	94.96	111.52		
C _{max} (ng/ml)		1664.52	1587.75	1.05	94.54	116.25		
Scaled								
Parameter	T/R Ratio	90% CI (%)		s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	1.04	94.78	112.56	0.0629901	0.2509782	-0.030652	Unscaled	PASS
AUC _∞	1.03	94.96	111.52	0.0684987	0.2617225	-0.035565	Unscaled	PASS
C _{max}	1.06	94.54	116.25	0.0829358	0.2879858	-0.035073	Unscaled	PASS

Erythromycin Ethylsuccinate for Oral Suspension USP, 1 x 400 mg/5 mL Fed Bioequivalence Study No. 740/17, N=53 (Male=53 and Female=0) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Unscaled								
Parameter (ng)		Test	RLD	Ratio	90% C.I.			
AUC _{0-t} (hr *ng/ml)		5668.92	6034.05	0.94	85.67	103.02		
AUC _∞ (hr *ng/ml)		5814.91	6178.13	0.94	85.91	103.11		
C _{max} (ng/ml)		1749.66	1974.02	0.89	79.37	98.98		
Scaled								
Parameter	T/R Ratio	90% CI (%)		s _{2wr}	s _{WR}	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	0.95	85.67	103.02	0.0605616	0.2460928	-0.022113	Unscaled	PASS
AUC _∞	0.95	85.91	103.11	0.0582925	0.2414384	-0.021623	Unscaled	PASS
C _{max}	0.89	79.37	98.98	0.0899009	0.2998348	-0.015517	Scaled/PE	PASS

The applicant conducted the dissolution testing using the same FDA-recommended method³ as their approved strength (200 mg/5 mL – 10 days in-use): 900 mL of pH 6.8 Sodium Phosphate Monobasic with 1% Sodium Lauryl Sulfate, with USP Apparatus II (Paddle) at 75 rpm. The applicant's dissolution method and data were reviewed separately and found adequate.⁴ The dissolution data are adequate with respect to supporting waiver request under 21 CFR 320.22 (d) (2) for the 200 mg/5 mL strength.

Per GDRP, OSIS recommends accepting data without on-site inspections for the clinical site (QPS Bioserve India Pvt. Limited)⁵ and the analytical site (b) (4) (b) (4).⁵ In addition, the studies submitted in the current supplement of ANDA 062055 do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status for the current ANDA is complete.

The application is **acceptable** with no deficiencies.

³ The dissolution method in the database for Erythromycin Ethylsuccinate Oral Suspension was adopted for this product, which is an oral granule for suspension.

⁴ GDRP, ANDA-062055-SUPPL-35»Biopharmaceutics Quality Review, ANDA 062055 S-35 biopharm review.docx, dated 8/28/2018.

<http://panorama.fda.gov/task/view?ID=5b0e349301f54dd6d7760dc0964d7eb3>

⁵ GDRP, ANDA-062055-SUPPL-35»

(b) (4)

(b) (4)

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use).
Reference Standard (RS) and Strength(s)	EryPed® (erythromycin ethylsuccinate for oral suspension) Oral Granules, 400 mg/5 mL
RS Holder; NDA/ANDA Number; Approval Date⁶	Arbor Pharmaceuticals LLC NDA 050207 04/02/1965
Reference Listed Drug (RLD) and Strength(s)	EryPed® (erythromycin ethylsuccinate for oral suspension) Oral Granules, 200 mg/5 mL and 400 mg/5 mL E.E.S.® (erythromycin ethylsuccinate for oral suspension) Oral Granules, 200 mg/5 mL
RLD Holder; NDA/ANDA Number; Approval Date⁶	Arbor Pharmaceuticals LLC NDA 050207 EryPed® 400 and E.E.S.® 200: 04/02/1965 EryPed® 200: 03/30/1987

3.2 PK/PD Information^{7,8}

Most recent RLD label (provide embedded document) Please check if an NG/G/J tube study is needed.	 EryPed label_04232018.pdf An NG/G/J tube study is not needed.
Indication	<p>To reduce the development of drug-resistant bacteria and maintain the effectiveness of EryPed® and other antibacterial drugs, EryPed® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.</p> <p>EryPed® is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:</p>

⁶ Online Orange Book, search: erythromycin ethylsuccinate, accessed on 6/18/2018.
https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=050207

⁷ Drugs@FDA, search: EryPed, assessed on 6/18/2018, label updated 04/23/2018.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/050207s074.050611s0361bl.pdf

⁸ <https://www.clinicalkey.com/pharmacology/monograph/226?sec=monind#dosage-limits>, accessed on 6/18/2018.

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae*, or *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of H. influenzae are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower-respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes*.

Listeriosis caused by *Listeria monocytogenes*.

Pertussis (whooping cough) caused by *Bordetella pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Diphtheria: Infections due to *Corynebacterium diphtheriae*, as an adjunct to antitoxin, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma: In the treatment of infections due to *Corynebacterium minutissimum*.

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute Pelvic Inflammatory Disease Caused by *Neisseria gonorrhoea*: As an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Syphilis Caused by *Treponema pallidum*: Erythromycin is an alternate choice of treatment for primary syphilis in penicillin-allergic patients. In primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Erythromycins are Indicated for the Treatment of the following Infections Caused by *Chlamydia*

	<p><i>trachomatis</i>: Conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to <i>Chlamydia trachomatis</i>.</p> <p>When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by <i>Ureaplasma urealyticum</i>.</p> <p>Legionnaires' Disease caused by <i>Legionella pneumophila</i>. Although no controlled clinical efficacy studies have been conducted, <i>in vitro</i> and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.</p> <p>Prophylaxis</p> <p>Prevention of Initial Attacks of Rheumatic Fever:</p> <p>Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of <i>Streptococcus pyogenes</i> infections of the upper respiratory tract, e.g., tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients. The therapeutic dose should be administered for 10 days.</p> <p>Prevention of Recurrent Attacks of Rheumatic Fever:</p> <p>Penicillin or sulfonamides are considered by the American Heart Association to be the drugs of choice in the prevention of recurrent attacks of rheumatic fever. In patients who are allergic to penicillin and sulfonamides, oral erythromycin is recommended by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).</p>
Boxed warning	N/A
Bioavailability	In general, oral bioavailability of erythromycin is poor. Erythromycin is readily inactivated by stomach acid, and several salts have been developed to overcome this drawback. Absorption takes place mainly in the duodenum.
Food Effect	Comparable serum levels of erythromycin are achieved in the fasting and non-fasting states.
T_{max}	Following single oral doses, peak serum levels of free erythromycin are achieved in 1-4 hours and range from 0.1-2 mcg/mL.
Metabolism	Erythromycin is an inhibitor of the CYP3A4 enzyme system as well as a substrate and inhibitor of P-glycoprotein (P-gp).

Excretion	Excretion of erythronycin is mainly via the bile, with some reabsorption. Only small amounts are found in the urine, with less than 5% excreted as unchanged drug.
Half-life	In adult patients with normal renal function, the serum half-life is about 1.5 hours.
Maximum Daily Dose	4 g erythronycin base/day

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	<p>The Product-Specific Guidance (PSG) for Erythronycin Ethylsuccinate for Oral Suspension was developed from New Guidance #2024647, Erythronycin ethylsuccinate Oral granule RLD 050207 New BE Guidance, 2024647 N050207 Erythronycin Ethylsuccinate Oral Granule BE Guidance ReviewYZFinal.doc, dated 4/5/2016. http://panorama.fda.gov/task/view?ID=564e447a00ad2a7dae3485fe5a658d31</p>  <p>PSG for Erythronycin Ethylsuccinate Oral Su (Recommended Jun 2016)</p>	
Summary of OGD or DB History	Approved ANDAs:	Yes
	Pending ANDAs:	Yes (b) (4) ANDA 062055 Supplement-034 & 035 (Current)
	Controls: ⁹	Yes, none is from the current applicant (ANI).
	Protocols: ¹⁰	Yes, #97-007 (b) (4) (b) (4)
	Pending Citizen Petitions and other legal and regulatory issues: ¹¹ If yes, please comment.	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No as of 09/10/2018.

Background:

Per the Orange book, there are no approved ANDAs currently available on the market for this RLD. There are two discontinued ANDAs for Erythromycin Ethylsuccinate Oral

⁹ OGD Control Database and Mercado, search: erythronycin or NDA 50207, accessed on 6/18/2018.

¹⁰ OGD-DB Protocols Tracking, search: erythronycin, accessed on 6/18/2018.

¹¹ Please check DLRS policy updates in the link <http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx>

Granules, EQ 200 mg base/5 mL: ANDA 062055 (approved 11/27/1978) by ANI Pharmaceuticals Inc. and ANDA 062305 (approved 12/18/1980) by Ross Laboratories Div Abbott Laboratories Inc.

The current ANDA 062055 for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL was approved on 11/27/1978, and discontinued for manufacturing in 2003.¹² ANI Pharmaceuticals, Inc. acquired the ownership of ANDA 062055 from Barr Laboratories Inc. (an indirect wholly owned subsidiary of Teva Pharmaceuticals USP, Inc. and Teva Pharmaceutical Industry Ltd.), effective 07/10/2015.¹³ The RLD product is Arbor Pharmaceuticals LLC's EryPed[®] (erythromycin ethylsuccinate for oral suspension) Oral Granules, 200 mg/5 mL and 400 mg/5 mL, and E.E.S.[®] (erythromycin ethylsuccinate for oral suspension) Oral Granules, 200 mg/5 mL (NDA 050207). The original ANDA 062055 (Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL – 10 days in-use) was approved referencing E.E.S.[®] (erythromycin ethylsuccinate for oral suspension) Oral Granules, 200 mg/5 mL.

The applicant submitted supplement-034 as a PAS on 12/22/2016 to obtain approval of new manufacturing, packaging, and testing facilities. A Complete Response Letter (CRL) was sent to the applicant on 09/20/2017 requesting the applicant to conduct a fasting BE study comparing their “post-change” test product to the reference product.¹⁴ On 02/14/2018, the applicant submitted a new fasting BE study (No. 606/17) comparing a new exhibit batch (No. MTMW12441) of the test product manufactured at the new facility to the RLD (Lot #1065393). The fasting study (No. 606/17) was found acceptable.¹⁵

Per the Product Specific Guidance (PSG) for Erythromycin Ethylsuccinate Oral Granules, the recommended analyte to measure is Erythromycin (free base and total) in plasma, and BE should be based on 90% CI of Erythromycin. Per the review of control #2024647,¹⁶ the reviewer recommended measuring erythromycin (free base and total) with bioequivalence based on erythromycin (free base). This distinction for which analyte bioequivalence is based on is not made in the current PSG for Erythromycin Ethylsuccinate Oral Granules.

¹² DARRTS, ANDA 062055, EDR, Annual Report-25 and Annual Report-26, Module 1.2 Cover Letter. [\\cdsesub1\evsprod\anda062055\0000\ml\us\cover.pdf](http://cdsesub1\evsprod\anda062055\0000\ml\us\cover.pdf)
[\\cdsesub1\evsprod\anda062055\0004\ml\us\cover-letter.pdf](http://cdsesub1\evsprod\anda062055\0004\ml\us\cover-letter.pdf)

¹³ DARRTS, ANDA 062055, COR-ANDAACK-01(Transfer of Ownership), dated 10/23/2015.

¹⁴ GDRP, ANDA-062055-SUPPL-34»Final Decision, AN62055DPM-SupplementCompleteResponseLetter34.doc, dated 9/20/2017.

<http://panorama.fda.gov/task/view?ID=585e17c500d7a7c481bda29800d4b6df>

¹⁵ GDRP, ANDA-062055-SUPPL-34-AMEND-94» Bioequivalence Discipline Review, A062055N034DB-SupplementReview01-Amend02142018.docx, dated 3/21/2018.

<http://panorama.fda.gov/task/view?ID=5a875a0e006598be1d4d7772d2cd12c2>

¹⁶ GDRP, CC #2024647, Erythromycin ethylsuccinate Oral granule RLD 050207 New BE Guidance, 2024647 N050207 Erythromycin Ethylsuccinate Oral Granule BE Guidance ReviewYZFinal.doc, dated 4/5/2016. <http://panorama.fda.gov/task/view?ID=564e447a00ad2a7dae3485fe5a658d31>

Erythromycin Ethylsuccinate is an ester of Erythromycin. Erythromycin Ethylsuccinate may be considered a prodrug of erythromycin since the ester must first be hydrolyzed to the free form to produce antimicrobial activity.¹⁷ Erythromycin ethylsuccinate itself is microbiologically inactive.

In ANDA 062055 supplements 034 and 035, the applicant only measured the total Erythromycin concentration by keeping the samples at 50°C in a water bath for 2 hours to convert Erythromycin Ethylsuccinate to Erythromycin (free base). BE was concluded based on 90% CI of Erythromycin (total).

(b) (4)

The applicant's analytical method of measuring only Erythromycin (total) and basing BE on 90% CI of Erythromycin (total) is deemed acceptable by the reviewer based on the following reasons:

- All approved ANDAs were approved based on total erythromycin measurement.
- Measuring and concluding BE based on total erythromycin is reliable.
- PK data for Erythromycin (total) is comparable to (b) (4)
- The two new strengths are qualitatively (Q1) to the approved strength, the amounts of the excipients (b) (4) for 35 days in-use. The manufacturing process is similar comparing to the approved strength.
- The current PSG for this drug product is not clear about which analyte to base BE.

Per an internal meeting dated 09/12/2018,¹⁹ the Office of Bioequivalence (OB) management reached consensus to accept the applicant's bioanalytical method of measuring Erythromycin (total) only and establishing BE based on 90% CI of Erythromycin (total). Therefore, the applicant's approach of only measuring Erythromycin (total) and BE based on 90% CI of Erythromycin (total) is acceptable.

Consult History:

On 06/21/2018, the Division of Bioequivalence (DB) II sent a consult to the Division of Clinical Review (DCR) inquiring if there are any safety concerns on the maximum daily intakes of Methylparaben and Polysorbate 80 in the applicant's proposed test formulation based on the maximum daily dose and the context of use of this drug product, particularly

¹⁷ Erythromycin Memorandum from Pharmacokinetics Evaluation Branch (HFN-226), DB Document Room, dated 7/17/87.

¹⁸ (b) (4)

¹⁹ [\\fda.gov\wod\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO2\BIO_Management_Meeting_Minutes\2018_Meeting_Minutes\Non-BMM Internal Meeting Minutes\2018.9.12.docx](https://www.fda.gov/wod/cder/ogd/all/ogds11/division/bio/bio2/bio_management_meeting_minutes/2018_meeting_minutes/non-bmm_internal_meeting_minutes/2018.9.12.docx)

for pediatric patients.²⁰ On 09/09/2018, the DCR responded to the consult request and concluded that the proposed levels of methylparaben and polysorbate 80 are acceptable from both Clinical and Pharmacology/Toxicology (Pharm/Tox) perspectives.²¹

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Module 5, 5.3.1.4, Appendix 16.6, Method Validation Report – page 01 of 58 to 58 of 58
Analyte	Erythromycin
Internal standard (IS)	Erythromycin-13CD3
Method description	Liquid Liquid Extraction method is optimized for quantification of Erythromycin A in K ₂ EDTA human plasma. (b) (4)
Limit of quantitation (ng/mL)	12.522
Average recovery of drug (%)	LQC: 77.08, MQC: 73.69, HQC: 77.04 Mean: 75.9
Average recovery of IS (%)	80.5
Standard curve concentrations (ng/mL)	12.522 to 6007.8
QC concentrations (ng/mL)	LLOQ QC: 12.581
	LQC: 32.677
	AQC-II: 200.47
	AQC-I: 1002.4

²⁰ GDRP, ANDA-062055-SUPPL-35»Bioequivalence IR and Consults, A062055N035DB-ConsultRequest01-DCR06212018.docx, dated 6/21/2018.

<http://panorama.fda.gov/task/view?ID=5b2bbe25004c711abe9ebdf61df52ec3>

²¹ GDRP, ANDA-062055-SUPPL-35»Bioequivalence IR and Consults, A062055N035DCR-ConsultReview01-Erythromycin syrup_methylparaben_Pediatric.pdf, dated 9/9/2018.

<http://panorama.fda.gov/task/view?ID=5b2bbe27004c717591db45e39d5d6ea9>

	MQC: 2403.8
	HQC: 4561.2
QC Intraday precision range (%)	LLOQ QC: 1.6 to 2.9
	LQC: 1.2 to 2.1
	AQC-II: 0.9 to 1.0
	AQC-I: 0.9
	MQC: 0.6
	HQC: 0.4 to 0.7
QC Intraday accuracy range (%)	LLOQ QC: 98.7 to 103.2
	LQC: 91.4 to 94.8
	AQC-II: 95.0 to 97.6
	AQC-I: 98.6 to 100.7
	MQC: 100.2 to 103.0
	HQC: 99.8 to 102.2
QC Inter day precision range (%)	LLOQ QC: 2.9
	LQC: 2.3
	AQC-II: 1.5
	AQC-I: 1.3
	MQC: 1.4
	HQC: 1.1
QC Inter day accuracy range (%)	LLOQ QC: 101.4
	LQC: 93.3
	AQC-II: 96.6
	AQC-I: 99.9
	MQC: 101.8
	HQC: 101.0
Bench-top stability (hrs)	15 hrs @ bench top (room temperature) condition
Stock stability (days)	10 days @ -20°C ± 10°C
Processed stability (hrs)	121 hrs @ auto sampler temperature (5°C)
Freeze-thaw stability (cycles)	Five Cycles @ -20°C ± 10°C and -70° ± 15°C
Long-term storage stability (days)	37 days @ -20°C ± 10°C and -70° ± 15°C
Dilution integrity	Concentration diluted 1/5 th and 1/10 th fold
Selectivity	No interference peaks noted in blank plasma samples

SOP for bioanalytical method validation submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? If not, was cross validation study conducted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No K ₂ EDTA
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Was the % recovery consistent across QC concentrations?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Comments on the Pre-Study Method Validation: Adequate

- The applicant submitted the following acceptable addendum to the method validation report # (b) (4)

Addendum I (06/04/2018)	Long term storage stability (-70°C ± 15°C and -20°C ± 10°C for 37 days) and OTC and Concomitant medications interference test for the quantification of Erythromycin A in K ₂ EDTA human plasma
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- The recommended analytes to measure in the PSG for this drug product is Erythromycin (free base and total) in plasma, and BE is based on 90% CI of Erythromycin. In the applicant's method, one of the sample extraction steps is "Keep the samples at 50°C in a water bath for 2 hrs for conversion of erythromycin ethyl succinate A to erythromycin A." Therefore, the applicant's method only measured the total erythromycin, which included contributions from erythromycin (free base) and erythromycin ethylsuccinate present in the plasma sample (after hydrolysis).

The applicant provided justification for measuring a single analyte (total erythromycin) and demonstrating BE based on total erythromycin in Module 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods.²² The applicant claimed that erythromycin ethylsuccinate is quite unstable in plasma and undergoes rapid hydrolysis (half-life under an hour) to erythromycin. The best metric representing the overall absorption of drug from an orally administered erythromycin ethylsuccinate product is total erythromycin (following hydrolysis), which includes contributions from erythromycin (free base) and erythromycin ethylsuccinate present in the plasma sample. The applicant's approach of only measuring Erythromycin (total) and BE based on 90% CI of Erythromycin (total) is acceptable. Please refer to [Section 3.3 OGD Recommendations for Drug Product](#) for detailed justifications.

²² ANDA 062055, EDR, dated 05/25/2018, Sequ 0020 (95), Module 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods, link: <\\cdsesub1\evsprod\anda062055\0020\m2\27-c lin-sum\summary-biopharm13.pdf>

3.5 In Vivo 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) (% CV)									Study Report Location
					C _{max} (ng/mL)	t _{max} (hr)	AUC _{0-tau} (hr*ng/mL)	AUC _∞ (hr*ng/mL)	t _{1/2} (hr)	k _{el} (hr ⁻¹)	k _{el} lower (hr)	k _{el} upper (hr)	AUC%Ext rap	
Study # 739/17	To assess the bioequivalence of Erythromycin Ethylsuccinate for Oral Suspension 400 mg/5 mL of ANI Pharmaceuticals, Inc., USA, comparing with that of EryPed® (Erythromycin Ethylsuccinate for Oral Suspension, 400 mg/5 mL) of Arbor Pharmaceuticals, Inc. Atlanta, GA 30328 in healthy, adult, human subjects under fasting conditions To monitor adverse events and ensure the safety of subjects.	Open label, balanced, randomized, two-treatment, three-period, three-sequence, single dose crossover, partial replicate oral bioequivalence study in healthy, adult, human subjects under fasting conditions	Test product (T): 01 unit dose Erythromycin Ethylsuccinate for Oral Suspension, USP 400 mg/5 mL Administered orally [Lot No. C-1127-72] Reference product (R): 01 unit dose EryPed® (Erythromycin Ethylsuccinate for Oral Suspension, USP 400 mg/5 mL) Administered orally [Lot No. 1074131]	58 (Completed) Healthy, male subjects Age: 28.9 (19.0 – 42.0)	1892.9 ± 881.65 (46.575)	0.63 (0.33 – 2.00)	7107.612 ± 3541.990 (49.834)	7650.205 ± 369.895 (48.311)	5.69 ± 3.68 (64.72)	0.1534 ± 0.0647 (42.1578)	8.58 ± 4.74 (55.23)	21.93 ± 3.77 (17.19)	7.004 ± 9.881 (141.082)	This information has been extracted from the Clinical Study Report (Pages 89 of 187 and 94 of 187)

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)	t _{max} (hr)	AUC _{0-tau} (hr*ng/mL)	AUC _∞ (hr*ng/mL)	t _{1/2} (hr)	K _{el} (hr ⁻¹)	K _{el lower} (hr)	K _{el upper} (hr)	AUC%Ext rap	
Study# 740/17	<p>To assess the bioequivalence of Erythromycin Ethylsuccinate for Oral Suspension 400 mg/5 mL of ANI Pharmaceuticals, Inc., USA comparing with that of EryPed® (Erythromycin Ethylsuccinate for Oral Suspension, 400 mg/5 mL) of Arbor Pharmaceuticals, LLC. Atlanta, GA 30328 in healthy, adult, human subjects under fed conditions.</p> <p>To monitor adverse events and ensure the safety of subjects</p>	Open label, balanced, randomized, two-treatment, three-period, three-sequence, single dose crossover, partial replicate oral bioequivalence study in healthy, adult, human subjects under fed conditions	<p>Test product (T): 01 unit dose Erythromycin Ethylsuccinate Granules 400 mg Base/5 mL</p> <p>Administered Orally [Lot No. C-1127-72]</p> <p>Reference product (R): 01 unit dose Eryped® (Erythromycin Ethylsuccinate Granules 400 mg Base/5 mL) Administered Orally. [Lot No. 1074131]</p>	53 (Completed) Healthy, male subjects Age: 30.7 (19.0 – 43.0)	2137.8 ± 1332.3 (62.318)	1.00 (0.25 – 3.50)	6980.978 ± 4369.838 (62.596)	7139.481 ± 4442.807 (62.229)	4.77 ± 1.97 (41.21)	0.1727 ± 0.0750 (43.4089)	9.49 ± 4.62 (48.71)	19.43 ± 4.94 (25.40)	2.502 ± 1.275 (50.966)	This information has been extracted from the Clinical Study report (Pages 92 of 166 and 96 of 166).

3.6 OSIS Status

Refer to comments in the [Executive Summary](#).

APPEARS THIS WAY ON ORIGINAL



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	739/17			
Study Title	An open label, balanced, randomized, two-treatment, three-period, three-sequence single dose, crossover, partial replicate oral bioequivalence study of Erythromycin Ethylsuccinate for Oral Suspension 400 mg/5 mL of ANI Pharmaceuticals, Inc., USA, comparing with that of EryPed® (Erythromycin Ethylsuccinate for Oral Suspension 400 mg/5 mL) of Arbor Pharmaceuticals, Inc. Atlanta, GA 30328 in healthy, adult, human subjects under fasting conditions.			
Study Type	<input checked="" type="checkbox"/> In Vivo BE	<input type="checkbox"/> In Vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Other (Specify)
Submission Location:				
Study Report	Module 5, 5.3.1.2, Clinical Study Report (Section 1.0 to Section 15.0)			
Validation Report	Module 5, 5.3.1.4, Appendix 16.6			
Bioanalytical Report	Module 5, 5.3.1.4, Appendix 15.5			
Clinical Site (Name, Address, Phone #, Fax #)	QPS Bioserve India Pvt. Limited, #6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India. Tel: +91-40-4377 0873 / 1875 Fax: +91-40-4377 0877			
Principal Clinical Investigator (Name, Email)	Dr. A. Sumanlata, MBBS, DLO, Dip. Hosp. Admn. E-mail: dr.sumanlata@qpsbioserve.com			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			
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) (b) Temperature Range	(17/02/2018 to 25/03/2018) 37 days -70°C ± 15°C			

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(e.g., -20° C to -80° C)	
Long-Term Storage Stability Coverage (no. days at temp °C)	37 days @ -20°C ± 10°C and -70°C ± 15°C
LTSS Data Location	LTSS study reports and data are presented in Module 5.3.1.4; Section Appendix 16.6 Method Validation Report, Page No.: 56 of 58 in the Addendum-I.

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Erythromycin Ethylsuccinate for Oral Suspension, USP 400 mg/5 mL	Ery-Ped® Granules (Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg per 5 mL)
Manufacturer	ANI Pharmaceuticals, Inc.	Arbor Pharmaceuticals, LLC.
Batch/Lot No.	C-1127-72	1074131
Manufacture Date	November 30, 2017	N/A
Expiration Date	N/A	January 18, 2020
Strength	400 mg/5 mL	400 mg/5 mL
Dosage Form	Oral Suspension	Oral Suspension
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency*	103.5%	101.9%
Content Uniformity (mean, % CV)	N/A	N/A
Dose Administered	1 × 400 mg Base/5 mL	1 × 400 mg Base/5 mL
Route of Administration	Oral	Oral

Are the test and reference products expired at the time of study? If Yes, please comment	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Is same bio-batch used in the dissolution and all BE studies? If No, please comment	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Is difference of the potency values for the Test and RLD within 5%?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

If No, please comment	
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4.1.1.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 60 Dosed: Period I: 60, Period II: 56 and Period III: 58 Completed: 58* Samples Analyzed: 60# Statistically Analyzed: 58
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	6 days
Randomization	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Blood Sampling Times	Pre-dose (0.0 hour) and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.50, 9.00, 11.00, 13.00, 16.00 and 24.00 hours post dose.
IRB Approval	<input checked="" type="checkbox"/> Yes Date: 02/09/2018 <input type="checkbox"/> No
Informed Consent	<input checked="" type="checkbox"/> Yes Date: 02/09/2018 <input type="checkbox"/> No
Length of Fasting	An overnight fast of at least 10 hours
Length of Confinement	In each period, the subjects were housed from at least 11 hours prior to drug administration to at least 24 hours after the drug administration.
Was the drug product administered per labeling for specialized dosage forms (e.g. ODT)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A Dosing instruction is in Section 9.4.1 Treatments Administered of the study report (page 49 of 187): \\cdsesub1\evsprod\anda062055\0020\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-no.-73917\fast-report.pdf
Safety Monitoring	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

* A total of 58 subjects completed the clinical phase of the study either all the periods or at least two periods (test once and reference once or reference twice). Subject (b) (6) did not turn up for period-II and period-III check-in. They only completed one period. Subject (b) (6) did not turn up for period-II check-in. They completed period I and period III.

Per the study protocol#P-739/17, all available samples were analyzed despite the subjects being withdrawn or dropped due to any reason and due to adverse events and only plasma concentration vs. time data for such subjects (b) (6) were presented in the study report, and were not included in pharmacokinetic and statistical analysis.

Comments on Study Design: Adequate

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. 739/17				
		Treatment Groups		
		Test Product (T) N = 58	Reference Product (R) N = 58	
Age (years)	Mean ± SD	28.9 ± 5.0	28.9 ± 5.0	
	Range	19.0 – 42.0	19.0 – 42.0	
Age Groups	< 18	00	00	
	18 – 40	56 (96.55%)	56 (96.55%)	
	41 – 64	02 (03.45%)	02 (03.45%)	
	65 – 75	00	00	
	> 75	00	00	
Sex	Male	58 (100.0%)	58 (100.0%)	
	Female	00	00	
Race	Asian	58 (100.0%)	58 (100.0%)	
	Black	00	00	
	Caucasian	00	00	
	Hispanic	00	00	
	Other	00	00	
BMI	Mean ± SD	24.7 ± 2.8	24.7 ± 2.8	
	Range	18.8 – 29.8	18.8 – 29.8	
Other Factors		NA	NA	

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
---	---

4.1.1.2.2 Dropout Information

Study No. 739/17				
Subject ID	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	Subject did not tum up for period-II and period-III check-in.	II & III	No	NA
	Subject did not tum up for period-II and period-III check-in.	II & III	No	NA
	Subject did not tum up for period-II check-in.	II	No	N/A
	Subject did not tum up for period-II check-in.	II	No	N/A

Are dropouts appropriate? If no, please comment.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups		
	Fasted Bioequivalence Study Study No. 739/17		
	Test (T) N = 58	Reference (R) N = 60	Post study N = 60
Nervous system disorders			
Dizziness	02 (3.45%)	01 (1.67%)	--
Gastrointestinal System			
Abdominal pain	02 (3.45%)	01 (1.67%)	--
Nausea	01 (1.72%)	--	--
Immune system disorders			
Eruptions over skin	01 (1.72%)	--	--
Investigations			
Decreased Haemoglobin	--	--	01 (1.67%)
Decreased HCT	--	--	01 (1.67%)
Total	06 (10.34%)	02 (3.33%)	02 (3.33%)

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)
N/A					

Were subjects who experienced vomiting included in statistical analysis?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
If yes, does the time of emesis exceed two times the median T _{max} value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Was the adverse event profile observed comparable for the test and reference product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Are there any serious adverse events or death?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Are there any other safety concerns based on the adverse event profile?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

4.1.1.2.4 Protocol Deviations

Study No. 739/17		
Type	Subject #s (Test)	Subject #s (Ref.)
In-house Blood Draw Deviation	Period-I	
	(b) (6)	
Subject Housing Deviations		
Physical Activity Restriction Deviations		

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	<input checked="" type="checkbox"/> Actual <input type="checkbox"/> Nominal
---	---

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
--	---

Concomitant Medications

Subject Number	Study Drug	Event	Medication given	Interaction with Study drug Pharmacokinetics	Medication given		Resolved	
					Date	Time	Date	Time
(b) (6)	Test	Eruptions over skin	Injection Avil 25 mg (Pheniramine Maleate 22.75 mg)	No	(b) (6)			
	Test	Abdominal pain	Injection Rantac 50 mg (Ranitidine 50 mg)	No				
		Nausea	Injection Zofer 4 mg (Ondansetron 4 mg)	No				
	Reference	Pain abdomen	Injection Rantac 50 mg (Ranitidine 50 mg)	No				
	Test	Pain abdomen	Injection Rantac 50 mg (Ranitidine 50 mg)	No				

Per the Micromedex database and the RLD label, the concomitant medications used during the study (Pheniramine Maleate, Ranitidine, and Ondansetron) do not have any drug interactions with the study drug (Erythromycin). In addition, in the method validation report for Erythromycin, Pheniramine Maleate, Ranitidine, and Ondansetron were validated to have no interferences with the study drug. Therefore, the reviewer agrees with the applicant that the concomitant medications used during the study did not impact the study outcome.

Comments on Clinical Results: Adequate

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)	Preparation and Qualification of Calibration Curve Standards and Quality Control Samples
		Bioanalytical Method Validation
		Chromatogram Acceptance Criteria
		Biosample Analysis and Within Study Validation
		Reanalysis of Study Samples
		Incurred Sample Reanalysis

All necessary SOPs submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
--------------------------------------	---

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No.: 739/17 Analyte Name: Erythromycin A										
Parameter	Standard Curve Samples									
	CC-01	CC-02	CC-03	CC-04	CC-05	CC-06	CC-07	CC-08	CC-09	CC-10
Concentration (ng/mL)	12.536	25.072	62.679	156.70	313.40	626.79	1567.0	3610.6	5405.0	6005.6
Inter day Precision (%CV)	1.0	2.0	2.2	1.4	1.3	1.2	1.3	1.3	0.9	1.4
Inter day Accuracy (%)	102.8	97.0	95.8	95.7	97.5	99.5	102.3	102.4	102.5	104.6
Linearity (Range of R ² values)	0.9964 to 0.9992									
Linearity Range (ng/mL)	12.536 to 6005.6									
Sensitivity/ LLOQ (ng/mL)	12.536									

Bioequivalence Study No. 739/17 Analyte Name: Erythromycin A					
Parameter	Quality Control Samples				
	HQC	MQC	AQC-I	AQC-II	LQC
Concentration (ng/mL)	4560.8	2403.5	1002.3	200.46	32.674
Interday Precision (%CV)	1.3	1.6	1.7	1.5	2.6
Interday Accuracy (% Actual)	103.0	103.1	100.3	96.9	95.8

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No No rejected runs.
Were 20% of chromatograms included?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Subject # (b) (6) (12 subjects out of 58 subjects)
Were chromatograms serially or randomly selected?	<input checked="" type="checkbox"/> serially <input type="checkbox"/> randomly
Any interfering peaks in chromatogram?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Were the chromatograms submitted by the firm acceptable?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Were 100% raw analytical data, including failed runs, provided?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.1.1.3.3 Reanalysis of Study Samples

Study No. 739/17 (Erythromycin A) Additional information in Volume (01 page), Page (47 of 59 pages)								
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 repeats	00	00	0.00	0.00	00	00	0.00	0.00
Inconsistent Internal Standard Response	11	05	0.86	0.20	11	05	0.86	0.20
Incomplete Analysis	00	01	0.00	0.04	00	01	0.00	0.04
Total	11	06	0.86	0.24	11	06	0.86	0.24

Note: Total number of test (T) samples analyzed: 1276
Total number of reference (R) samples analyzed: 2552

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
If no, is recalculation of PK parameters necessary?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Did recalculation of PK parameters change the study outcome?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

Comments on Bioanalytical Results: Adequate

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters – Reviewer Calculated

		Test		Reference 1		Reference 2		RatioT1R1	RatioT1R2	RatioR1R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T1/R1)	(T1/R2)	(R1/R2)
AUCT	ng hr/mL	7108.267	49.82	7027.711	38.97	6364.112	46.40	1.01	1.12	1.10
AUCI	ng hr/mL	7650.907	48.30	7586.253	38.94	7054.811	46.40	1.01	1.08	1.08
C _{MAX}	ng/mL	1892.948	46.58	1965.525	41.26	1642.246	46.81	0.96	1.15	1.20
T _{MAX} *	hr	0.625	.	0.500	.	0.500	.	1.25	1.25	1.00
KE	hr ⁻¹	0.153	42.16	0.139	38.48	0.148	51.56	1.10	1.04	0.94
THALF	hr	5.692	64.75	5.983	54.76	5.996	59.30	0.95	0.95	1.00

Composite				
Parameter	Unit	Test	Reference (Mean of R1 and R2)	Ratio T/R
AUCT	ng hr/mL	7108.267	6695.912	1.06
AUCI	ng hr/mL	7650.907	7320.532	1.05
C _{MAX}	ng/mL	1892.948	1803.886	1.05
T _{MAX} *	hr	0.625	0.500	1.25
KE	hr ⁻¹	0.153	0.144	1.07
THALF	hr	5.692	5.990	0.95

* T_{max} values are presented as median.

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Erythromycin Ethylsuccinate for Oral Suspension USP 1 x 400 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fasting Bioequivalence Study No. 739/17								
Unscaled								
Parameter (ng)	Test	N	RLD	N	Ratio	90% C.I.		
AUC _{0-t} (hr *ng/ml)	6222.352	58	6024.106	114	103.29	94.78	112.56	
AUC _∞ (hr *ng/ml)	6752.840	58	6562.013	111	102.91	94.96	111.52	
C _{max} (ng/ml)	1664.518	58	1587.750	114	104.84	94.54	116.25	
Scaled								
Parameter	T/R Ratio	90% CI (%)		s2wr	sWR	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	103.66	94.78	112.56	0.062990	0.25098	-0.0307	UNSCALED	Bioequivalent
AUC _∞	103.23	94.96	111.52	0.068499	0.26172	-0.0356	UNSCALED	Bioequivalent
C _{max}	105.81	94.54	116.25	0.082936	0.28799	-0.0351	UNSCALED	Bioequivalent

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Erythromycin Ethylsuccinate for Oral Suspension USP 1 x 400 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fasting Bioequivalence Study No. 739/17								
Unscaled								
Parameter (ng)	Test	N	RLD	N	Ratio	90% C.I.		
AUC _{0-t} (hr *ng/ml)	6222.35	58	6024.11	114	1.03	94.78	112.56	
AUC _∞ (hr *ng/ml)	6752.84	58	6562.01	111	1.03	94.96	111.52	
C _{max} (ng/ml)	1664.52	58	1587.75	114	1.05	94.54	116.25	
Scaled								
Parameter	T/R Ratio	90% CI (%)		s2wr	sWR	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	1.04	94.78	112.56	0.0629901	0.2509782	-0.030652	Unscaled	PASS
AUC _∞	1.03	94.96	111.52	0.0684987	0.2617225	-0.035565	Unscaled	PASS
C _{max}	1.06	94.54	116.25	0.0829358	0.2879858	-0.035073	Unscaled	PASS

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	AUC _t : 0.2823 AUC _i : 0.2767 C _{max} : 0.3343
Is there a T_{max} difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including T _{max} analysis, for substantial difference)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No The median T _{max} T/R ratio is 1.25, and the median T _{max} difference (T-R) is 0.125 hour.
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Are there first measurable drug concentration as C_{max}? If yes, please comment	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Are there C_{max} at the first time point? If yes, is the study (sample) design adequate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	58	0.93	0.47	0.99
Reference 1	55	0.93	0.52	0.99
Reference 2	56	0.92	0.39	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	See table below. The reviewer examined the plasma concentration-time profiles for these subjects in the respective periods, and concluded that the sampling time schedule is adequate.			

SUBJ	PER	TRT	AUC _t /AUC _i
(b) (6)	3	2	0.79
	1	2	0.79
	3	1	0.47
	2	1	0.73
	3	2	0.60
	1	1	0.75
	3	2	0.39
	1	2	0.75
	3	2	0.80
	1	2	0.73
	3	2	0.79

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(b) (6)	1	2	0.52
	3	1	0.73
	1	1	0.56
	2	2	0.73

Comments on PK results: Adequate

- The applicant claimed that subject (b) (6) is an outlier based on studentized residual test, and the applicant also conducted statistical analysis excluding subject (b) (6) in addition to including this subject. Both results passed the BE criteria. The final report includes the results including the outlier and the results excluding the outlier are provided as supportive data. As the Agency does not recommend excluding statistically detected outliers, the reviewer agrees with the applicant's decision of including subject (b) (6) in the statistical analysis.

4.1.1.5 Overall Comment

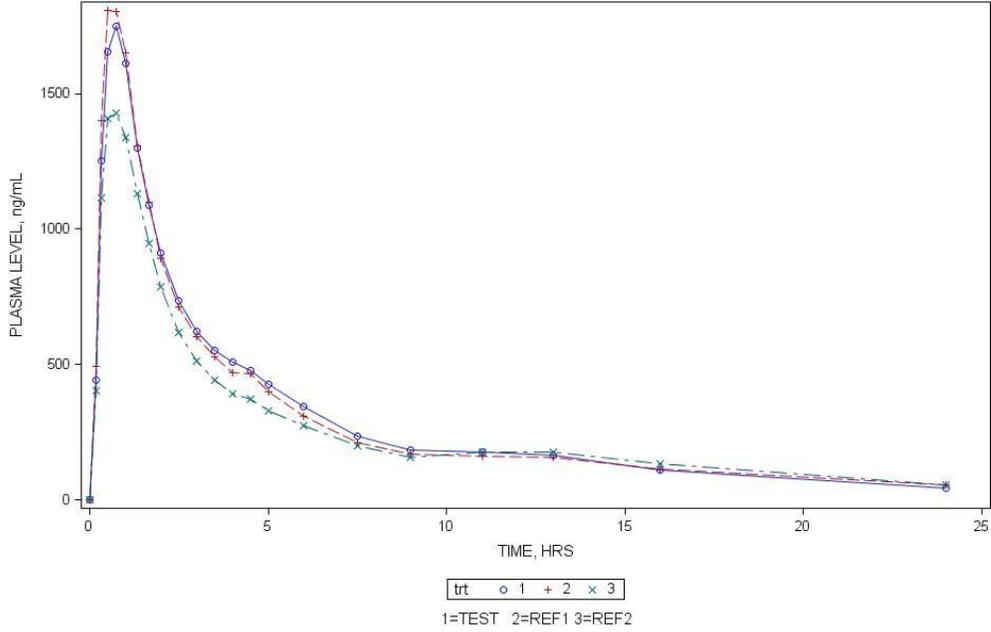
Was the Fasting bioequivalence study acceptable? Yes.

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

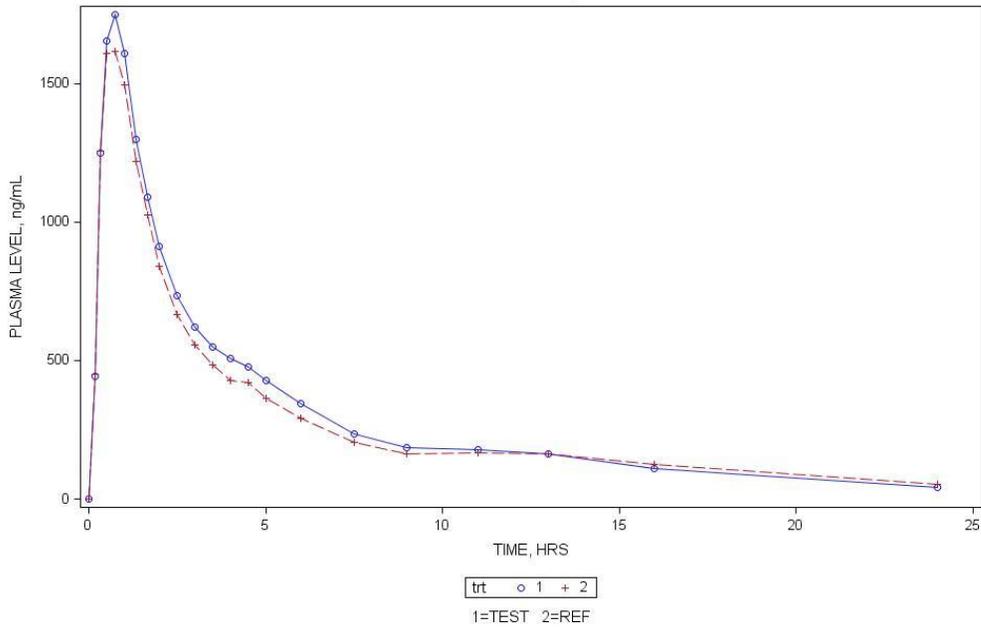
Time (hr)	Test (n=58)		Reference 1 (n=57)		Reference 2 (n=57)		RatioT1R1	RatioT1R2	RatioR1R2
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T1/R1)	(T1/R2)	(R1/R2)
0.00	0.00	.	0.00	.	0.00
0.17	442.59	87.46	493.61	84.18	404.31	105.61	0.90	1.09	1.22
0.33	1250.49	57.57	1398.72	51.30	1115.72	72.07	0.89	1.12	1.25
0.50	1653.53	48.28	1807.82	44.27	1409.37	55.08	0.91	1.17	1.28
0.75	1748.80	51.71	1804.39	45.01	1427.28	51.09	0.97	1.23	1.26
1.00	1609.79	54.90	1652.09	47.48	1339.66	52.67	0.97	1.20	1.23
1.33	1299.18	53.84	1305.07	50.11	1129.20	55.97	1.00	1.15	1.16
1.67	1088.63	55.64	1100.95	51.58	946.99	60.66	0.99	1.15	1.16
2.00	912.87	59.97	892.99	52.96	786.83	62.12	1.02	1.16	1.13
2.50	735.21	61.74	713.56	52.03	619.60	62.81	1.03	1.19	1.15
3.00	622.74	62.06	604.11	51.31	512.38	62.45	1.03	1.22	1.18
3.50	550.26	61.92	528.86	51.07	442.13	62.33	1.04	1.24	1.20
4.00	507.23	62.19	469.16	52.15	390.19	62.78	1.08	1.30	1.20
4.50	478.21	57.35	465.52	50.43	372.04	61.66	1.03	1.29	1.25
5.00	427.83	58.18	398.41	49.47	329.56	57.45	1.07	1.30	1.21
6.00	344.79	64.56	310.49	49.72	272.76	61.43	1.11	1.26	1.14
7.50	235.88	70.02	211.26	49.03	201.99	64.54	1.12	1.17	1.05
9.00	185.26	65.01	166.93	52.05	158.33	64.10	1.11	1.17	1.05
11.00	177.16	71.09	160.64	59.76	176.09	58.67	1.10	1.01	0.91
13.00	164.24	82.01	155.20	75.60	174.71	70.78	1.06	0.94	0.89
16.00	111.56	91.42	115.72	97.68	132.41	76.70	0.96	0.84	0.87
24.00	43.11	111.28	56.05	166.46	53.76	95.66	0.77	0.80	1.04

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Mean concentration-nominal time profiles
PLASMA Erythromycin Ethylsuccinate LEVELS
Erythromycin Ethylsuccinate for Oral Suspension, ANDA 062055
UNDER FASTING CONDITIONS
DOSE= 1 x 400 mg/5 mL



Mean concentration-nominal time profiles
PLASMA Erythromycin Ethylsuccinate LEVELS
Erythromycin Ethylsuccinate for Oral Suspension, ANDA 062055
UNDER FASTING CONDITIONS
DOSE= 1 x 400 mg/5 mL



4.1.2 Single-Dose Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	740/17			
Study Title	An open label, balanced, randomized, two-treatment, three-period, three-sequence, single dose, crossover, partial replicate oral bioequivalence study of Erythromycin Ethylsuccinate Granules 400 mg Base/5 mL of ANI Pharmaceuticals, Inc., USA, comparing with that of EryPed® (Erythromycin Ethylsuccinate Granules 400 mg Base/5 mL) of Arbor Pharmaceuticals, Inc. Atlanta, GA 30328 in healthy, adult, human subjects under fed conditions.			
Study Type	<input checked="" type="checkbox"/> In Vivo BE	<input type="checkbox"/> In Vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Other (Specify)
Submission Location:				
Study Report	Module 5, 5.3.1.2, Clinical Study Report (Section 1.0 to Section 15.0)			
Validation Report	Module 5, 5.3.1.4, Appendix 16.6			
Bioanalytical Report	Module 5, 5.3.1.4, Appendix 15.5			
Clinical Site (Name, Address, Phone #, Fax #)	QPS Bioserve India Pvt. Limited, #6-56/6/1A, Opp: IDPL Factory, Balanagar, Hyderabad-500 037, Telangana, India. Tel: +91-40-4377 0873 / 1875 Fax: +91-40-4377 0877			
Principal Clinical Investigator (Name, Email)	Dr. A. Sumanlata, MBBS, DLO, Dip. Hosp. Admn. E-mail: dr.sumanlata@qpsbioserve.com			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			
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) (b) Temperature Range (e.g., -20° C to -80° C)	(21/02/2018 to 24/03/2018) 32 days -70°C ± 15°C			
Long-Term Storage Stability Coverage (no.	37 days @ -20°C ± 10°C and -70°C ± 15°C			

days at temp °C)	
LTSS Data Location	LTSS study reports and data are presented in Module 5.3.1.4; Section: Appendix 16.6 Method Validation Report, Page No.: 56 of 58 in the Addendum-I.

4.1.2.1.2 Product Information

Same as the fasting study.

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 60 Dosed: Period I: 59, Period II: 54 and Period III: 50 Completed: 53* Samples Analyzed: 60# Statistically Analyzed: 53
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	Period-I and period-II: 4 days Period-II and period-III: 6 days
Randomization	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Blood Sampling Times	Pre-dose (0.0 hour) and at 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.50, 10.00, 12.00, 14.00, 16.00 and 24.00 hours post dose.
IRB Approval	<input checked="" type="checkbox"/> Yes Date: 02/09/2018 <input type="checkbox"/> No
Informed Consent	<input checked="" type="checkbox"/> Yes Date: 02/09/2018 <input type="checkbox"/> No
Length of Fasting	In each period, all the subjects were fasted for at least 10 hours prior to start of standardized high fat and high calorie breakfast which was served to all the subjects 30 minutes prior to drug administration.
Length of Confinement	In each period, the subjects were housed from at least 11 hours prior to drug administration to at least 24 hours after the drug administration.
Was the drug product administered per labeling for specialized dosage forms (e.g. ODI)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A Dosing instruction is in Section 9.4.1 Treatments Administered of the study report (page 50 of 166): \\cdsesub1\evsprod\anda062055\0020\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-no.-74017\fed-report.pdf
Safety Monitoring	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

* A total of 53 subjects completed the clinical phase of the study either all the periods or at least two periods (test once and reference once or reference twice). Subjects (b) (6) were withdrawn either due to AE or noncompliance. Subject (b) (6) did not turn up for period-III check-in. They completed period I and period II. Therefore, they were included in the statistical analysis.

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Per the study protocol#P-740/17, all available samples were analyzed despite the subjects being withdrawn or dropped due to any reason and due to adverse events and only plasma concentration vs. time data for such subjects (subjects # (b) (6)) were presented in the study report, and were not included in pharmacokinetic and statistical analysis.

Standard FDA Meal ²³ Used?		<input type="checkbox"/> Yes		<input checked="" type="checkbox"/> No	
If No, then meal components and composition is listed in the tables below.					
Composition of Non-standard FDA Meal Used in Fasting Bioequivalence Study (Study No. 740/17)					
Ingredients	Amount (g)	Energy (K Cal)	Protein (K Cal)	Fat (K Cal)	Carbohydrate (K Cal)
Bread toast with butter	34g of bread with 20g of butter	234.01	11.24	148.05	74.72
Egg omelet	27	96.87	15.96	80.91	---
Fried chicken	72	171.77	77.72	94.05	---
Potato cutlet	110	281.55	9.60	136.35	135.6
Milk	240 mL	157.14	34.56	72.9	49.68
TOTAL		941.34	149.08	532.26	260.00
PERCENTAGE		100	15.84	56.54	27.62

Comments on Study Design: Adequate

- Washout periods of 4 days and 6 days are adequate considering the half-life of the drug is about 1.5 hours for adult patients with normal renal function.

²³ If the standard meal referenced in the CDER Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies is used, then it is not necessary to complete the table. In that case, please add a statement in the fed bioequivalence study report indicated that the "FDA standard meal" was used. If an alternative meal is used, then please complete the above summary table.

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Study No. 740/17			
		Treatment Groups	
		Test Product (T) N = 53	Reference Product (R) N = 53
Age (years)	Mean ± SD	30.7 ± 5.9	30.7 ± 5.9
	Range	19.0 – 43.0	19.0 – 43.0
Age Groups	< 18	00	00
	18 – 40	51 (96.23%)	51 (96.23%)
	41 – 64	02 (03.77%)	02 (03.77%)
	65 – 75	00	00
	> 75	00	00
Sex	Male	53 (100.0%)	53 (100.0%)
	Female	00	00
Race	Asian	53 (100.0%)	53 (100.0%)
	Black	00	00
	Caucasian	00	00
	Hispanic	00	00
	Other	00	00
BMI	Mean ± SD	24.5 ± 3.1	24.5 ± 3.1
	Range	18.7 – 29.7	18.7 – 29.7
Other Factors		NA	NA

<p>Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
--	---

4.1.2.2.2 Dropout Information

Study No. 740/17				
Subject ID	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	Subject was withdrawn from the study due to adverse event (Vomiting) after dosing in period-I. He was withdrawn at 09:14 hours on (b) (6) for treatment reference (R).	I	No	NA
(b) (6)	Subject was withdrawn from the study due to adverse event (Vomiting) after dosing in period-I. He was withdrawn at 10:55 hours on (b) (6) for treatment (T).	I	No	NA
(b) (6)	Subject did not turn up for period-III check-in.	III	No	NA
(b) (6)	Subject was withdrawn from the study due to adverse event (Vomiting) after dosing in period-I. He was withdrawn at 10:07 hours on (b) (6) for treatment test (T).	I	No	NA
(b) (6)	Subject was withdrawn from the study due to adverse event (Vomiting) after dosing in period-I. He was withdrawn at 10:20 hours on (b) (6) for treatment reference (R).	I	No	NA
(b) (6)	Subject was withdrawn from the study due to adverse event (Vomiting) after dosing in period-I. He was withdrawn at 09:57 hours on (b) (6) for treatment reference (R).	I	No	NA
(b) (6)	Subject did not turn up for period-III check-in.	III	No	NA
(b) (6)	Subject was withdrawn from the study due to noncompliance to high fat and high calorie breakfast in period-I. He was withdrawn at 09:32 hours on (b) (6)	I	No	NA
(b) (6)	Subject was withdrawn from the study due to adverse event (Vomiting) after dosing in period-II. He was withdrawn at 11:05 hours on (b) (6) for treatment test (T).	II	No	NA
(b) (6)	Subject did not turn up for period-III check-in.	III	No	NA

Are dropouts appropriate? If no, please comment.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
--	---

4.1.2.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups		
	Fed Bioequivalence Study Study No. 740/17		
	Test (I) N = 56	Reference (R) N = 57	Post study N = 59
Gastrointestinal System			
Vomiting	03 (5.36%)	03 (5.26%)	--
Nausea	--	03 (5.26%)	--
Abdominal distension	--	01 (1.75%)	--
Skins and subcutaneous disorders			
Rashes over the fore head	--	01 (1.75%)	--
Investigations			
Decreased Haemoglobin	--	--	02 (3.39%)
Decreased HCT	--	--	02 (3.39%)
Increased Total Bilirubin	--	--	01 (1.69%)
Increased SGOT	--	--	01 (1.69%)
Total	03 (5.36%)	08 (14.04%)	06 (10.17%)

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)	R	I	(b) (6)	(b) (6)	0.60	
	T	I		(b) (6)		1.03
	T	I		(b) (6)		0.22
	R	I		(b) (6)		0.73
	R	I		(b) (6)		0.32
	T	II		(b) (6)		1.40

Were subjects who experienced vomiting included in statistical analysis?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A Per the protocol, all the subjects listed in the table above vomited within 2 times median Tmax of Erythromycin ($2 \times 2.0 = 4.0$ hrs) following drug administration. Therefore, they were excluded from statistical analysis.
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.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Was the adverse event profile observed comparable for the test and reference product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Are there any serious adverse events or death?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Are there any other safety concerns based on the adverse event profile?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

4.1.2.2.4 Protocol Deviations

Study No. 740/17		
Type	Subject #s (Test)	Subject #s (Ref.)
There were no protocol deviations reported in this study.		

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.	<input checked="" type="checkbox"/> Actual <input type="checkbox"/> Nominal
--	---

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
---	---

Concomitant Medications

Subject Number	Study Drug	Event	Medication given	Interaction with Study drug Pharmacokinetics	Medication given		Resolved	
					Date	Time	Date	Time
(b) (6)	Reference	Nausea	Injection Zofer 4 mg (Ondansetron 4 mg)	No	(b) (6)			
	Reference	Nausea	Injection Zofer 4 mg (Ondansetron 4 mg)	No				
	Reference	Vomiting	Injection Zofer 4 mg (Ondansetron 4 mg)	No				
	Reference	Nausea	Injection Zofer 4 mg (Ondansetron 4 mg)	No				
		Abdominal distension	Injection Rantac 50 mg (Ranitidine 50 mg)	No				
	Reference	Rashes over the fore head	Injection Avil 25 mg (Pheniramine Maleate 22.75 mg)	No				

Among the subjects received concomitant medications, subject (b) (6) was withdrawn from the study due to an AE (vomiting). Per the Micromedex database and the RLD label, the concomitant medications used during the study (Pheniramine Maleate, Ranitidine, and Ondansetron) do not have any drug interactions with the study drug (Erythromycin). In addition, in the method validation report for Erythromycin, Pheniramine Maleate, Ranitidine, and Ondansetron were validated to have no interferences with the study drug. Therefore, the reviewer agrees with the applicant that the concomitant medications used during the study did not impact the study outcome.

Comments on Clinical Results: Adequate

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Same as the fasting study.

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No.: 740/17 Analyte Name: Erythromycin A										
Parameter	Standard Curve Samples									
	CC-01	CC-02	CC-03	CC-04	CC-05	CC-06	CC-07	CC-08	CC-09	CC-10
Concentration (ng /mL)	12.536	25.072	62.679	156.70	313.40	626.79	1567.0	3610.6	5405.0	6005.6
Inter day Precision (%CV)	1.5	3.2	1.9	2.1	1.6	1.4	1.1	1.0	1.4	1.5
Inter day Accuracy (%)	103.5	95.9	94.4	95.3	96.6	98.6	101.6	102.4	104.0	107.4
Linearity (Range of R ² values)	0.9940 to 0.9988									
Linearity Range (ng/mL)	12.536 to 6005.6									
Sensitivity/ LLOQ (ng/mL)	12.536									

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Single-Dose Fed Bioequivalence Study Review

Bioequivalence Study No. 740/17 Analyte Name: Erythromycin A					
Parameter	Quality Control Samples				
	HQC	MQC	AQC-I	AQC-II	LQC
Concentration (ng/mL)	4560.8	2403.5	1002.3	200.46	32.674
Interday Precision (%CV)	1.5	1.5	1.9	2.0	4.6
Interday Accuracy (% Actual)	102.8	102.1	99.5	96.1	94.6

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No No rejected runs.
Were 20% of chromatograms included?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Subject (b) (6), (b) (6) (12 subjects out of 53 subjects)
Were chromatograms serially or randomly selected?	<input checked="" type="checkbox"/> serially <input type="checkbox"/> randomly
Any interfering peaks in chromatogram?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Were the chromatograms submitted by the firm acceptable?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Were 100% raw analytical data, including failed runs, provided?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.1.2.3.3 Reanalysis of Study Samples

Study No. 740/17 (Erythromycin A) Additional information in Volume (02 pages), Pages (48 of 60 to 49 of 60 pages)								
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 repeats	00	00	0.00	0.00	00	00	0.00	0.00
Inconsistent Internal Standard Response	12	11	1.02	0.48	12	11	1.02	0.48
Incomplete Analysis	00	01	0.00	0.04	00	01	0.00	0.04
Above Upper Limit of Quantification	00	01	0.00	0.04	00	01	0.00	0.04
Poor Chromatography	00	01	0.00	0.04	00	01	0.00	0.04

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Single-Dose Fed Bioequivalence Study Review

Total	12	14	1.02	0.60	12	14	1.02	0.60
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Note: Total number of test (T) samples analyzed: 1182
Total number of reference (R) samples analyzed: 2296

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
If no, is recalculation of PK parameters necessary?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Did recalculation of PK parameters change the study outcome?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A

Comments on Bioanalytical Results: Adequate

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters - Reviewer Calculated

Parameter	Unit	Test		Reference 1		Reference 2		RatioT1R1	RatioT1R2	RatioR1R2
		Mean	CV%	Mean	CV%	Mean	CV%	(T1/R1)	(T1/R2)	(R1/R2)
AUCT	ng hr/mL	6980.978	62.60	7349.722	57.30	6893.865	54.20	0.95	1.01	1.07
AUCI	ng hr/mL	7139.484	62.23	7495.131	57.04	7052.143	53.98	0.95	1.01	1.06
C _{MAX}	ng/mL	2137.822	62.32	2440.928	53.59	2214.270	54.18	0.88	0.97	1.10
T _{MAX} *	hr	1.000	.	0.750	.	0.750	.	1.33	1.33	1.00
KE	hr ⁻¹	0.173	43.41	0.175	40.35	0.171	39.26	0.99	1.01	1.02
THALF	hr	4.775	41.21	4.588	36.61	4.694	37.35	1.04	1.02	0.98

Composite				
Parameter	Unit	Test	Reference (Mean of R1 and R2)	Ratio T/R
AUCT	ng hr/mL	6980.978	7121.794	0.98
AUCI	ng hr/mL	7139.484	7273.637	0.98
C _{MAX}	ng/mL	2137.822	2327.599	0.92
T _{MAX} *	hr	1.000	0.750	1.33
KE	hr ⁻¹	0.173	0.173	1.00
THALF	hr	4.775	4.641	1.03

* T_{max} values are presented as median.

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Erythromycin Ethylsuccinate for Oral Suspension USP 1 x 400 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study No. 740/17								
Unscaled								
Parameter (ng)	Test	N	RLD	N	Ratio	90% C.I.		
AUC _{0-t} (hr *ng/ml)	5668.922	53	6034.049	103	93.95	85.67	103.02	
AUC _∞ (hr *ng/ml)	5814.906	53	6178.131	103	94.12	85.91	103.11	
C _{max} (ng/ml)	1749.657	53	1974.024	103	89.30	79.37	98.98	
Scaled								
Parameter	T/R Ratio	90% CI (%)		s2wr	sWR	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	94.52	85.67	103.02	0.06056	0.24609	-0.0221	UNSCALED	Bioequivalent
AUC _∞	94.80	85.91	103.11	0.05829	0.24144	-0.0216	UNSCALED	Bioequivalent
C _{max}	89.30	79.37	98.98	0.08990	0.29983	-0.0155	SCALED	Bioequivalent

4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Erythromycin Ethylsuccinate for Oral Suspension USP 1 x 400 mg/5 mL Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study No. 740/17								
Unscaled								
Parameter (ng)	Test	N	RLD	N	Ratio	90% C.I.		
AUC _{0-t} (hr *ng/ml)	5668.92	53	6034.05	103	0.94	85.67	103.02	
AUC _∞ (hr *ng/ml)	5814.91	53	6178.13	103	0.94	85.91	103.11	
C _{max} (ng/ml)	1749.66	53	1974.02	103	0.89	79.37	98.98	
Scaled								
Parameter	T/R Ratio	90% CI (%)		s2wr	sWR	Criteria Bound	Method Used	Outcome
		Lower	Upper					
AUC _{0-t}	0.95	85.67	103.02	0.0605616	0.2460928	-0.022113	Unscaled	PASS
AUC _∞	0.95	85.91	103.11	0.0582925	0.2414384	-0.021623	Unscaled	PASS
C _{max}	0.89	79.37	98.98	0.0899009	0.2998348	-0.015517	Scaled/PE	PASS

4.1.2.4.4 Additional Information for the Study

Root Mean Square Error (RMSE)	AUC _t : 0.2889 AUC _i : 0.2850 C _{max} : 0.3484
Is there a T _{max} difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including T _{max} analysis, for substantial difference).	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No The median T _{max} T/R ratio is 1.33, and the median T _{max} difference (T-R) is 0.25 hour. The difference is minor, and the reviewer deems it acceptable.
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Are there first measurable drug concentration as C _{max} ? If yes, please comment.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Subject ^{(b) (6)} had first measurable drug concentration as C _{max} in Period-I (Test) and Period-II (Ref). The early sampling schedule (e.g. 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00 hrs etc.) is adequate. The first measurable C _{max} did not impact the PK results.
Are there C _{max} at the first time point? If yes, is the study (sample) design adequate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	53	0.97	0.93	0.99
Reference 1	53	0.98	0.93	0.99
Reference 2	50	0.98	0.94	0.99
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

4.1.2.5 Overall Comment

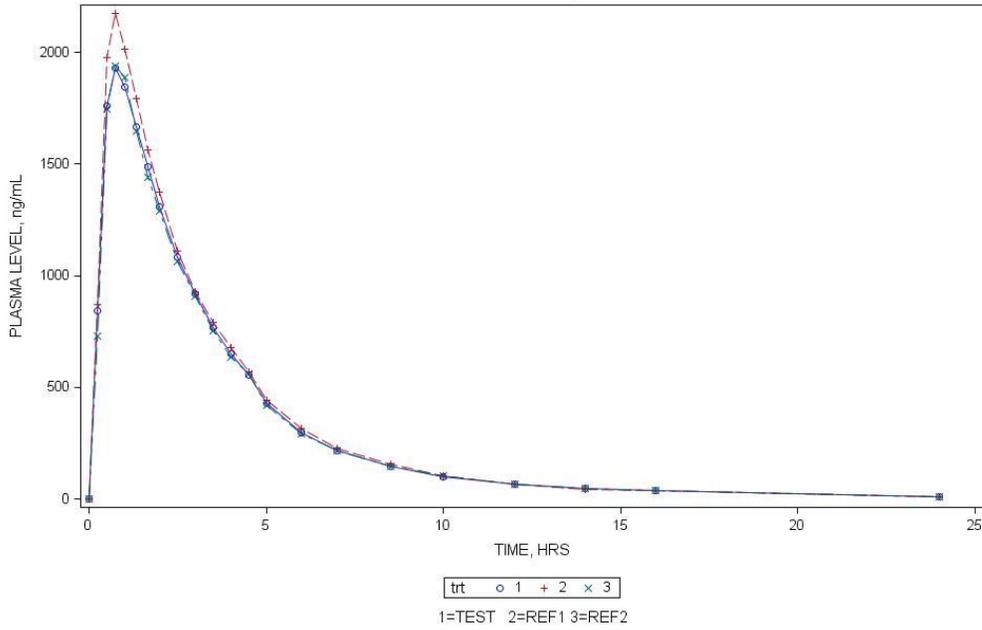
Was the Fed bioequivalence study acceptable? Acceptable.

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

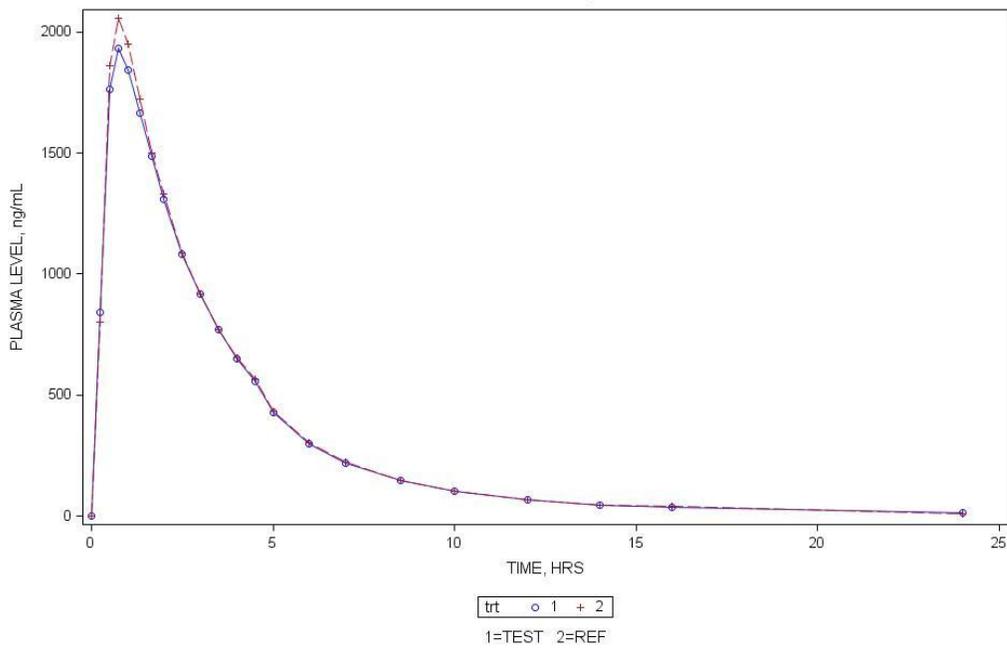
Time (hr)	Test (n=53)		Reference 1 (n=53)		Reference 2 (n=50)		RatioT1R1	RatioT1R2	RatioR1R2
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T1/R1)	(T1/R2)	(R1/R2)
0.00	0.00	.	0.00	.	0.00
0.25	843.36	96.80	871.95	88.08	732.35	96.36	0.97	1.15	1.19
0.50	1761.10	73.40	1977.02	67.15	1747.46	70.71	0.89	1.01	1.13
0.75	1931.67	67.81	2175.65	62.05	1939.08	62.71	0.89	1.00	1.12
1.00	1843.96	67.13	2015.50	58.73	1888.09	57.47	0.91	0.98	1.07
1.33	1666.59	62.20	1795.57	56.53	1649.24	52.18	0.93	1.01	1.09
1.67	1486.11	58.49	1563.88	55.10	1438.49	49.62	0.95	1.03	1.09
2.00	1308.08	58.20	1372.97	54.69	1290.15	50.71	0.95	1.01	1.06
2.50	1082.35	58.43	1109.83	56.26	1064.72	52.99	0.98	1.02	1.04
3.00	916.74	59.58	927.30	56.94	907.42	53.66	0.99	1.01	1.02
3.50	769.97	62.33	789.90	63.26	753.88	55.09	0.97	1.02	1.05
4.00	651.23	64.83	677.32	70.19	636.67	60.03	0.96	1.02	1.06
4.50	557.48	67.01	572.40	70.96	561.60	66.47	0.97	0.99	1.02
5.00	428.48	67.51	442.13	69.91	421.73	65.56	0.97	1.02	1.05
6.00	299.63	71.89	314.97	71.28	290.90	66.12	0.95	1.03	1.08
7.00	218.29	71.29	228.78	70.88	216.98	71.92	0.95	1.01	1.05
8.50	146.69	73.54	154.38	71.83	145.29	67.89	0.95	1.01	1.06
10.00	101.57	74.03	106.61	75.93	102.45	69.43	0.95	0.99	1.04
12.00	67.48	79.58	68.99	76.85	67.63	75.62	0.98	1.00	1.02
14.00	46.38	81.92	45.13	79.54	47.43	83.53	1.03	0.98	0.95
16.00	38.17	81.26	38.04	80.57	39.93	87.11	1.00	0.96	0.95
24.00	12.05	122.65	10.84	122.38	11.29	132.69	1.11	1.07	0.96

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Mean concentration-nominal time profiles
PLASMA Erythromycin Ethylsuccinate LEVELS
Erythromycin Ethylsuccinate for Oral Suspension, ANDA 062055
UNDER Fed CONDITIONS
DOSE= 1 x 400 mg/5 mL



Mean concentration-nominal time profiles
PLASMA Erythromycin Ethylsuccinate LEVELS
Erythromycin Ethylsuccinate for Oral Suspension, ANDA 062055
UNDER Fed CONDITIONS
DOSE= 1 x 400 mg/5 mL



4.2 Formulation Data

4.2.1 Test Formulation

Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL		
Ingredient	Amount (mg) / Unit	Amount (%) / Unit
Erythromycin Ethylsuccinate USP		(b) (4)
Lactose Anhydrous (Anhydrous)(b) (4)		
Methylparaben, NF		
Sodium Citrate Anhydrous, USP		
Povidone, USP (b) (4)		
Simethicone, USP		
Flavor – (b) (4) Cherry (b) (4)		
Polysorbate 80, NF		
Sucrose, NF (b) (4)		
Total		(b) (4)

Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL		
Ingredient	Amount (mg) / Unit	Amount (%) / Unit
Erythromycin Ethylsuccinate USP		(b) (4)
Lactose Anhydrous (Anhydrous)(b) (4)		
Methylparaben, NF		
Sodium Citrate Anhydrous, USP		
Povidone, USP (b) (4)		
Simethicone, USP		
Flavor – (b) (4) Cherry (b) (4)		
Polysorbate 80, NF		
Sucrose, NF (b) (4)		
Total		(b) (4)



Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If no, are they all within IIG (per day) limits?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
If no, are additional data or Pharm/Tox consult necessary?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A



	A Clinical and Pharm/Tox consult was sent to the DCR regarding the acceptability of the applicant's proposed levels for Methylparaben and Polysorbate 80 in the test formulation, particularly for pediatric patients. ²² See comments below for details.
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)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Are all strengths of the test formulation acceptable?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Per DCR's consult response dated 09/09/2018,²¹ "*The proposed levels of methylparaben (b) (4) and polysorbate 80 (b) (4) in the current generic erythromycin ethylsuccinate oral suspension are acceptable from both Clinical and P/T perspectives.*" The BE reviewer agrees with DCR's conclusion.

Comments on Formulation: Adequate

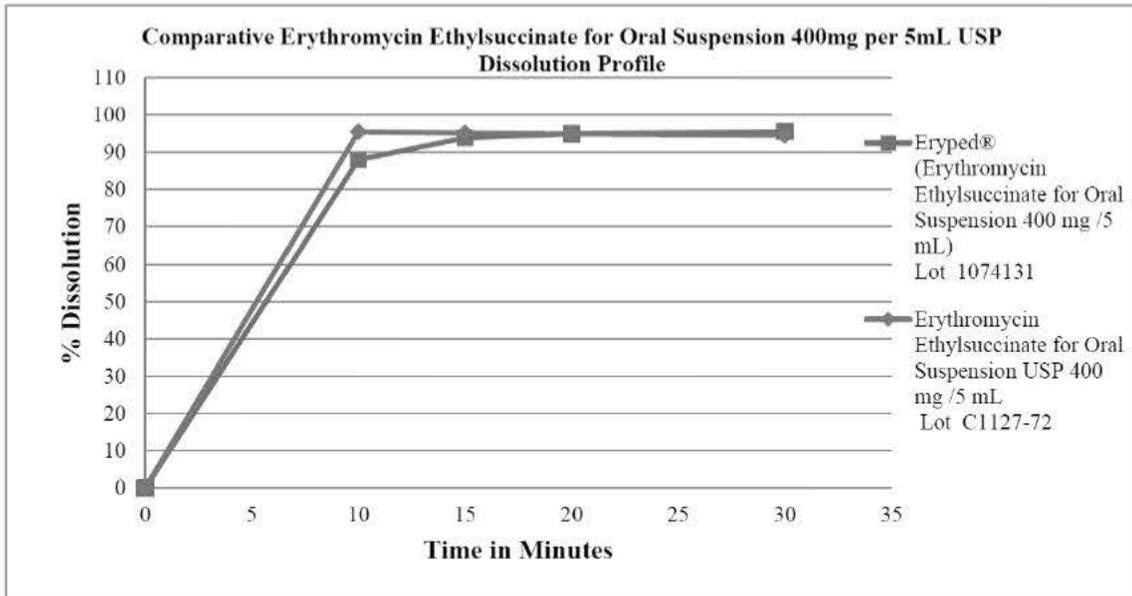
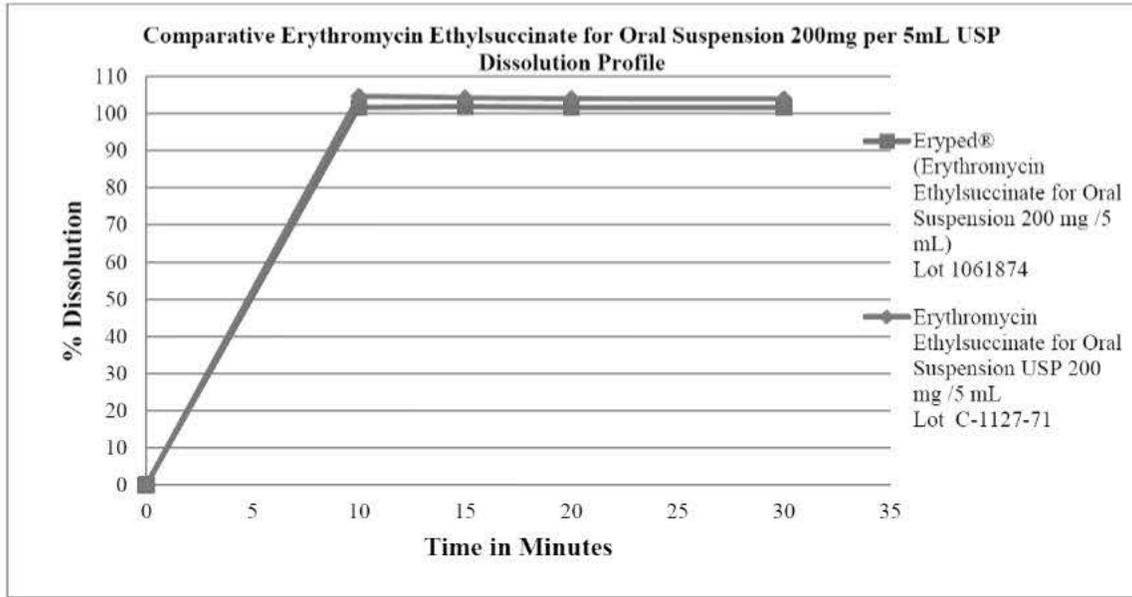
4.3 Dissolution Testing

4.3.1 Dissolution Data

Dissolution Conditions		Apparatus:	USP II								
		Speed of Rotation:	75 rpm								
		Medium:	pH 6.8 Sodium Phosphate Monobasic with 1% Sodium Lauryl Sulfate								
		Volume:	900 mL								
		Temperature:	37.0°C ± 0.5°C								
Firm's Proposed Specifications		Not Less Than (NLT)	(b) (4) % (Q) in 20 minutes								
Dissolution Testing Site (Name, Address)		ANI Pharmaceuticals, Inc. 210 Main Street West Baudette, MN 56623									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Dt.) (Reference – Exp. Dt.)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)					Study Report Location
						0	10	15	20	30	
Study Report #: N/A	May 2, 2018	Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL Batch No.: C-1127-71 Mfg Date: Nov. 29, 2017	200 mg/5 mL Suspension	12	Mean (%)	0	105	104	104	104	3.2.P.5.4
					Range (%)	(b) (4)					
					%CV	0	0.4	0.3	0.3	0.3	
Study Report #: N/A	May 3, 2018	Ery-Ped® (Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL) Batch No.: 1061874 Exp. Date: May 2019	200 mg/5 mL Suspension	12	Mean (%)	0	102	102	102	102	3.2.P.5.4
					Range (%)	(b) (4)					
					%CV	0	0.5	0.4	0.5	0.5	

Dissolution Conditions		Apparatus:	USP II								
		Speed of Rotation:	75 rpm								
		Medium:	pH 6.8 Sodium Phosphate Monobasic with 1% Sodium Lauryl Sulfate								
		Volume:	900 mL								
		Temperature:	37.0°C ± 0.5°C								
Firm's Proposed Specifications		Not Less Than (NLT)	(b) (4) % (Q) in 20 minutes								
Dissolution Testing Site (Name, Address)		ANI Pharmaceuticals, Inc. 210 Main Street West Baudette, MN 56623									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Dt.) (Reference – Exp. Dt.)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)					Study Report Location
						0	10	15	20	30	
Study Report #: N/A	January 26, 2018	Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL Batch No.: C-1127-72 Mfg Date: Nov. 30, 2017	400 mg/5 mL Suspension	12	Mean (%)	0	96	95	95	95	3.2.P.5.4
					Range (%)	(b) (4)					
					%CV	0	2.0	1.9	1.9	1.9	
Study Report #: N/A	November 26, 2017	Ery-Ped® (Erythromycin Ethylsuccinate for Oral Suspension USP, 400 mg/5 mL) Batch No.: 1074131 Exp. Date: January 2020	400 mg/5 mL Suspension	12	Mean (%)	0	88	94	95	96	3.2.P.5.4
					Range (%)	(b) (4)					
					%CV	0	2.7	1.6	1.6	1.6	

4.3.2 Dissolution Profiles



4.3.3 F2 Metric

F2 metric calculated?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If no, reason why F2 not calculated	Very rapidly dissolving (b) (4)

Please comment on whether dissolution data are adequate to support requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).	Adequate per 21 CFR 320.22 (d) (2)
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Overall Comments: Adequate

- The applicant conducted the dissolution testing using the same FDA-recommended method as their approved strength (200 mg/5 mL – 10 days in-use): 900 mL of pH 6.8 Sodium Phosphate Monobasic with 1% Sodium Lauryl Sulfate, with USP Apparatus II (Paddle) at 75 rpm. The dissolution method in the database for Erythromycin Ethylsuccinate Oral Suspension was adopted for this product, which is an oral granule for suspension. The UPS monograph for this drug product does not specify a dissolution testing method.²⁹ Per the FDA’s external dissolution database, the applicant should develop a dissolution method for this drug product.³⁰ The applicant’s dissolution method and data were reviewed separately found adequate.⁴
- The dissolution data are adequate with respect to supporting waiver request under 21 CFR 320.22 (d) (2) for the 200 mg/5 mL strength.

4.4 Attachments

4.4.1 Additional Studies

<p>Are there any additional studies? (e.g. pilot, failed) If yes, please provide the location of report (complete/summary)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
--	--

4.4.2 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting	 062055SUPP35fasting Data.xlsx	 HV-RefScale3Period-ver3-ParamNotConve	N/A	 062055-ANALYSIS.doc
		 BE03-For3PerHVDSu mmaryTables with nex	 062055_FASTING_stat_Erythromycin Ethylsu	 062055_FASTING_table_Erythromycin Ethyls
Fed	 A062055SUPP035fed Data.xlsx	 HV-RefScale3Period-ver3-ParamNotConve	N/A	 062055-ANALYSIS.doc
		 BE03-For3PerHVDSu mmaryTables with nex	 062055_Fed_stat_Erythromycin Ethylsuccina	 062055_Fed_table_Erythromycin Ethylsuccina

²⁹ UPS 40-NF 35 Online, search: Erythromycin Ethylsuccinate for Oral Suspension, accessed on 6/19/2018.

³⁰ FDA’s external dissolution database, search: Erythromycin Ethylsuccinate, updated 6/30/2016, accessed on 6/19/2018.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 062055-SUPP-035

APPLICANT: ANI Pharmaceuticals, Inc.

DRUG PRODUCT: Erythromycin Ethylsuccinate for Oral Suspension, USP, Eq 200 mg base/5 mL (35 Day In-Use) and Eq 400 mg base/5 mL (35 Day In-Use)

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 062055

Completed Assignment for 062055 ID: 36449

Reviewer: Wang, Yibo

**Date
Completed:**

Verifier: ,

**Date
Verified:**

Division: Division of Bioequivalence

Erythromycin Ethylsuccinate for Oral Suspension, USP,

Description: Eq 200 mg base/5 mL (35 Day In-Use) and Eq 400 mg
base/5 mL (35 Day In-Use)

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
36449	5/25/2018	BIO	Supplement [1]	1	1
36449	5/25/2018	BIO	Consult Review (For Consults to Other Office) [1]	1	1
36449	5/25/2018	Parallel	Fasting Study (Full template) [1]	1	1
36449	5/25/2018	Parallel	Fed Study (Full Template) [1]	1	1
36449	5/25/2018	Parallel	Dissolution-Based Waiver (IR) (For all waiver strengths) [0.25]	0.25	0.25
36449	5/25/2018	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
				Total:	5.25

BIOPHARMACEUTICS REVIEW			
Office of New Drugs Products			
Application No.	ANDA 062055 S-35	Primary Reviewer: Jia Yin, Ph.D.	
Division	CDER/OPQ/ONDP/Biopharmaceutics		
Responsible Organization	Office of Generic Drugs	Secondary Reviewer: Poonam Delvadia, Ph.D.	
Applicant	ANI Pharmaceuticals, Inc.	Biopharmaceutics Branch Chief: Kimberly Raines, Ph.D.	
Product Name	Erythromycin Ethylsuccinate for Oral Suspension USP	Biopharmaceutics Division Director: Paul Seo, Ph.D.	
Indication	Treatment of infections caused by susceptible strains of the designated organisms in diseases	Date Assigned	8/21/2018
Formulation/strength	Granule for oral suspension, 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use) (Proposed)	Date of Review	8/21/2018
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date(s)	Date of informal/formal consult	GDUFA due date	
May 25, 2018	N/A	September 24, 2018	
Type of Submission	Prior Approval Supplement (PAS)		
Key Review Points	<p>The supplement proposes: Addition of new strengths 200 mg/5mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use)</p> <p>Biopharmaceutics review focuses on: Proposed dissolution method and acceptance criterion for finished product batch release and stability testing</p>		
Recommendation	ADEQUATE		
<u>SUMMARY</u>			
<i>Background</i>			
The reference listed drug (RLD) for erythromycin ethylsuccinate granule for oral suspension 200			

mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use) is ERY-PED[®] developed by Arbor Pharms LLC. The RLD was approved in 1965 under NDA 050207. Under the same NDA, there is another drug product E.E.S.[®] (erythromycin ethylsuccinate granule for oral suspension 200 mg/5 mL, 10 Day In-Use). The sole generic product for E.E.S.[®] by Barr Laboratories, Inc. (an indirect, wholly owned subsidiary of Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.) was approved under ANDA 062055 in 1978 and the manufacturing was discontinued in 2003.¹ In 2015, ANI Pharmaceuticals Inc. acquired the ownership of the ANDA 062055 and submitted supplement 34 (PAS) to relaunch the generic drug product equivalent to the E.E.S.[®] granules (200 mg/5 mL, 10 Day In-Use) at new manufacturing, packaging, and testing facilities.

Submission

This supplement (S-35) is for the addition of two drug product strengths (200 mg/5 mL and 400 mg/5 mL), the generic version for the ERY-PED[®] product line under the same ANDA. This submission contains information on chemistry, manufacturing, control of erythromycin ethylsuccinate granule for oral suspension 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use) and a pivotal bioequivalence (BE) study on 400 mg/5 mL (35 Day In-Use) strength under both fasted and fed condition. In addition, the Applicant is requesting biowaiver for the lower strength, 200 mg/5 mL (35 Day In-Use). The review of biowaiver is under the purview of the office of generic drugs (OGD) and is found adequate.

Review Objective

The biopharmaceutics assessment focuses on the proposed dissolution method and acceptance criterion for the proposed drug product for finished product batch release and stability testing.

Biopharmaceutics Assessment

The proposed in vitro dissolution method for the proposed 35 Day In-Use products is the same as the that for erythromycin ethylsuccinate granule for oral suspension 200 mg/5 mL (10 Day In-Use). The dissolution method for the 10 Day In-Use product is found to be acceptable in the Biopharmaceutics review for ANDA 062055 S-34-A-94. The formulation of the proposed 35 Day In-Use products is based on the formulation of the 10 Day In-Use product. They have the same API and the same excipients, (b) (4) for the proposed 35 Day In-Use products. The manufacturing process for both the approved 10 Day In-Use and the proposed 35 Day In-Use products are also similar. From a biopharmaceutics perspective, the proposed dissolution method is acceptable.

¹ ANDA-062055-SUPPL-34: [Biopharmaceutics Review of A062055-S34](#) (Accessed on 05/04/2018)

The proposed dissolution acceptance criterion NLT $\frac{(b)}{(4)}\%$ (Q) in 20 min is supported by dissolution data.

Recommendations

The proposed in vitro dissolution method and acceptance criterion for the proposed drug product have been assessed and determined to be adequate. From a biopharmaceutics perspective, ANDA 062055 S-35 for erythromycin ethylsuccinate granule for oral suspension 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use) is recommended for APPROVAL.

<p>Signature</p> <p>Jia Yin Ph.D Biopharmaceutics Reviewer Office of New Drug Products</p>	<p>Signature</p> <p>08/28/2018 Poonam Delvadia, Ph.D., Acting Biopharmaceutics Lead DB\ONDP\OPQ</p>
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BIOPHARMACEUTICS ASSESSMENT

Dissolution Method and Acceptance Criterion

The dissolution method and acceptance criterion for erythromycin ethylsuccinate granule for oral suspension 200 mg/5 mL (10 Day In-Use) was evaluated in the Biopharmaceutics review for ANDA 062055 S-34-A-94 and found to be acceptable.² The same dissolution method and acceptance criterion (**Table 1**) is proposed for these two new strengths 200 mg/5 mL (35 Day In-Use) and 400 mg/5mL (35 Day In-Use).

Table 1 Proposed dissolution method and acceptance criterion for finished product batch release and stability testing of the proposed product^{3, 4}

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times (min)	Acceptance criterion
FDA Database*	II (Paddle)	75 rpm	Monobasic sodium phosphate buffer pH 6.8 containing 1% Sodium dodecyl sulfate (SDS)/ 37°C ± 0.5°C	900 mL	10, 15, 20, 30	20 min – NLT $\frac{(b)}{(4)}\%$ (Q)

² <http://panorama.fda.gov/task/view?ID=5a875a0f00659b489a6edd80c04e0ee3>

³ [Application 062055 - Sequence 0020 - 3.2.P.2 Pharmaceutical Development -](#)

⁴ [Application 062055 - Sequence 0020 - 3.2.P.5.1 Specification\(s\) -](#)

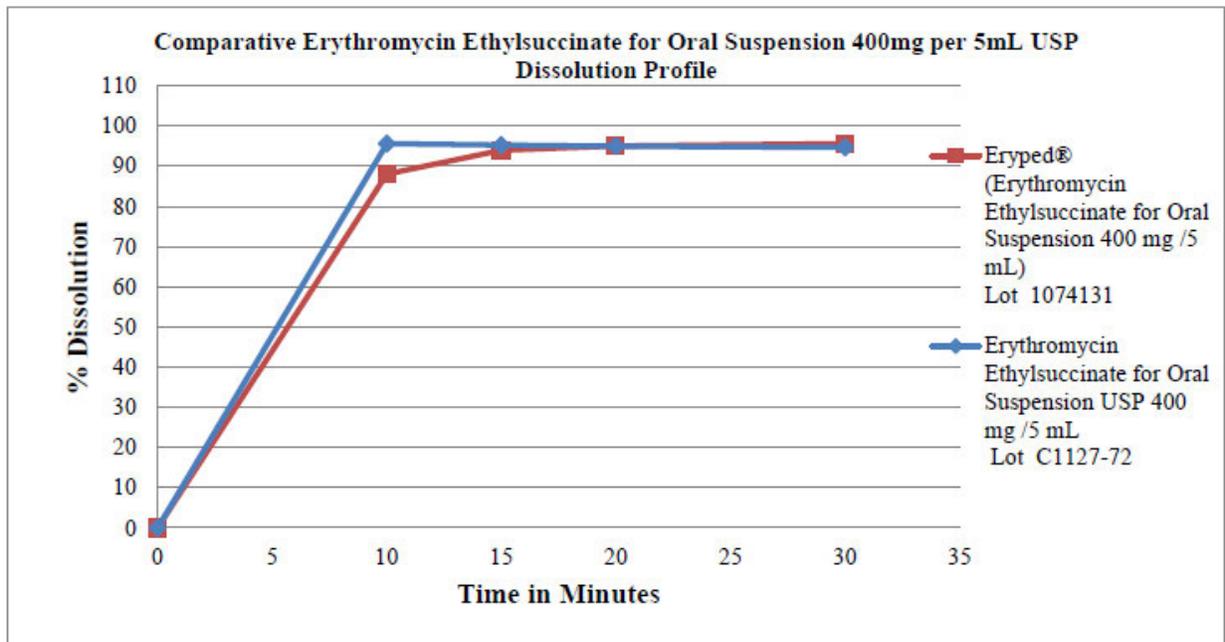
* Dissolution method in the database for oral suspension was adopted for this product which is oral granule for suspension

Dissolution Data

Comparative dissolution data are provided for the test product and the RLD (ERY-PED®) at each strength. Dissolution comparison is also made between lower strength 200 mg/5 mL (35 Day In-Use) and higher strength 400 mg/5 mL (35 Day In-Use) test products. Detailed dissolution data are available at [Application 062055 - Sequence 0020 - 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods - .](#) Test product (Lot No. C-1127-72) and ERY-PED® (Lot No. 1074131) at 400 mg/5 mL (35 Day In-Use) strength level are used in the pivotal BE study, the mean dissolution profiles of which are shown in **Figure 1**.

As **Figure 1** indicates, the release of both the biobatch and the RLD is rapid and reaches completion in (b) (4). Similar dissolution profiles are observed for the lower strength product as well.

Figure 1 Dissolution comparison between test product (Lot No. C-1127-72) and ERY-PED® (Lot No. 1074131) at 400 mg/5 mL (35 Day In-Use) strength level (Pivotal biobatches)



Stability data for exhibit batches at both strengths are provided for up to 3 months under both accelerated and long-term conditions.⁵ All dissolution tests have met the proposed dissolution acceptance criterion and no significant change in dissolution is observed.

⁵ [Application 062055 - Sequence 0020 - 3.2.P.8.3 Stability Data -](#)

Risk Management of Formulation and Process Variables

During the initial risk assessment of formulation variables, drug substance particle size distribution was identified as a high-risk factor for drug release. The Applicant used the same drug substance particle size specification as that for the erythromycin ethylsuccinate granule for oral suspension 200mg/5 mL (10 Day In-Use). No additional drug substance particle size options were evaluated.

No manufacturing process variables were identified as a high-risk factor for drug release.

Assessment

Dissolution method: Acceptable

The proposed in vitro dissolution method for the proposed 35 Day In-Use products is the same as the that for erythromycin ethylsuccinate granule for oral suspension 200 mg/5 mL (10 Day In-Use). The dissolution method for the 10 Day In-Use product is found to be acceptable in the Biopharmaceutics review for ANDA 062055 S-34-A-94. The formulation of the proposed 35 Day In-Use products is based on the formulation of the 10 Day In-Use product. They have the same API and the same excipients, (b) (4) for the proposed 35 Day In-Use products. The manufacturing process for both the 10 Day In-Use and the proposed 35 Day In-Use products are also similar. From a biopharmaceutics perspective, the proposed dissolution method is acceptable.

Dissolution acceptance criterion: Adequate

The proposed dissolution acceptance criterion NLT (b) (4) % (Q) in 20 min is supported by dissolution data.

Conclusion/Recommendation

The proposed in vitro dissolution method and acceptance criterion for the proposed drug product have been assessed and determined to be adequate. From a biopharmaceutics perspective, ANDA 062055 S-35 for erythromycin ethylsuccinate granule for oral suspension 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use) is recommended for APPROVAL.



Poonam
Delvadia

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Date: 8/28/2018 04:03:21PM
GUID: 5388edae000671a12787e2fcf4cde1bb



Jia
Yin

Digitally signed by Jia Yin
Date: 8/28/2018 04:02:21PM
GUID: 58b87f98014440ef24056beabf77e491

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-035

OTHER REVIEWS

CLINICAL & PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)

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

Erythromycin Ethylsuccinate for Oral Suspension USP, EQ 200 mg base/5 mL and EQ 400 mg base/5 mL (35 Day in-use)

Drug Product:	Erythromycin Ethylsuccinate for Oral Suspension USP, EQ 200 mg base/5 mL and EQ 400 mg base/5 mL (35 Day in-use)
ANDA#/Applicant:	ANDA 062055/ANI Pharmaceuticals Inc. (Originally approved on 11/27/1978)
RLD#/Approval Date:	NDA 050207 (Approved on 07/14/1981)
Sponsor:	Arbor Pharmaceuticals LLC
Pharmacology-Toxicology Primary Reviewer:	Xin Fu, PhD, DABT Pharmacologist
Pharmacology-Toxicology Secondary Reviewer:	Sruthi King, PhD Lead Pharmacologist
Clinical Primary Reviewer:	Sarah Yim, MD Director, Supervisory Medical Officer
Tertiary Reviewer:	Sarah Yim, MD Director, Supervisory Medical Officer
To:	Ethan Stier, PhD, RPh., Director, Division of Bioequivalence 2, OGD
Reason for Consult:	To determine the safety of methylparaben and polysorbate 80 at (b) (4) of the proposed drug formulation, respectively, particularly in pediatric populations.
Date of Submission:	05/25/2018
Date Consult Received:	06/21/2018
Date of Completion:	09/09/2018
Conclusion:	DCR concludes that the proposed levels of methylparaben and polysorbate 80 are acceptable from both Clinical and Pharmacology/Toxicology (P/T) perspectives. See Section 2 for Internal Recommendations. There is nothing to be conveyed to the applicant.
Deficiency Classification:	<input type="checkbox"/> Major <input type="checkbox"/> Minor <input checked="" type="checkbox"/> N/A (Review is Adequate)

1 Executive Summary:

This review addresses a consult request from Division of Bioequivalence of OGD, to determine the safety of maximum daily intakes (MDI) of methylparaben and polysorbate 80 in the proposed Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL (35 Day In-Use) and Eq 400 mg base/5 mL (35 Day In-Use) in supplement S035 of ANDA 062055, which is a prior approval supplement (PAS). Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5mL (also identified and referred to as "10 Day In-Use in supplement S035) was first approved under ANDA 062055 on 11/27/1978. The reference listed drug (RLD) was E.E.S.® (erythromycin ethylsuccinate for oral suspension) Oral Granules, 200 mg/5 mL from NDA 050207 when ANDA 062055 was first approved. The proposed MDIs are (b) (4) for methylparaben and (b) (4) for polysorbate 80, depending on age and body weight.

The RLD identified for the proposed two new strengths is EryPed® (Erythromycin Ethylsuccinate for Oral Suspension, USP), 400 mg/5 mL & 200 mg/ 5 mL with In-Use shelf life of 35 days stored at room temperature in NDA 050207. According to the RLD labeling, the maximum daily dose (MDD) varies among different age/body weight groups, ranging 2 mg/kg/day in neonates to 4 g/day in adults. [NOT FOR FOIA] RLD does not contain methylparaben. The level of polysorbate 80 level in RLD is (b) (4) (b) (4) in the proposed generic formulations.

Both methylparaben and polysorbate 80 are common excipients widely used in various oral drug products indicated in both pediatric and adult patients, and also have a long history of use in food, cosmetics, and other products with widespread human exposure. (b) (4) (b) (4)

(b) (4).¹ Therefore, there is no safety concern with the proposed use of polysorbate 80 in the 35 Day In-Use formulation.

Although the RLD does not contain methylparaben, its MDI in the proposed drugs does not exceed FDA approved drugs with similar context of use (e.g., similar oral route, patient age groups, treatment duration) for most of the indicated patient populations, except for the neonate group. Therefore, the neonatal population was the focus of this safety assessment.

The potential safety concern with parabens are endocrine disrupting effects resulting in potential reproductive and developmental toxicity. Methylparaben has been shown to have estrogenic activity *in vitro* and *in vivo* in nonclinical studies. No human toxicity findings are available to confirm the nonclinical findings, although human exposures are to methylparaben levels required for its preservative effects, which are much lower. (b) (4)

¹ (b) (4)

(b) (4)

(b) (4) Therefore, DCR concludes the proposed (b) (4) level of methylparaben is acceptable.

In summary, the proposed levels of methylparaben (b) (4) and polysorbate 80 (i.e., (b) (4) in ANDA 062055's erythromycin ethylsuccinate oral suspension (35-day in-use) drug products are acceptable from both Clinical and Pharmacology/Toxicology (P/T) perspectives.

2 Internal Recommendation:

The proposed levels of methylparaben (b) (4) and polysorbate 80 (b) (4) in the current generic erythromycin ethylsuccinate for oral suspension, 200 mg/5 mL (35 Day In-Use) and 400 ng/5 mL (35 Day In-Use) are acceptable from both Clinical and P/T perspectives.

3 Comments to be conveyed by the RPM to the Applicant:

There is no comment to be conveyed to the applicant.

4 Regulatory Background:

Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5mL (also started being identified and referred as "10 Day In-Use in supplement S035) was first approved under ANDA 062055 on 11/27/1978. The reference listed drug (RLD) was E.E.S.® (erythromycin ethylsuccinate for oral suspension) Oral Granules, 200 mg/5 mL from NDA 050207 when it was first approved.

On 05/25/2018, the applicant submitted supplement S035 as a Prior Approval Supplement (PAS) to add two new strengths to this ANDA, i.e., Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use), which "*is qualitatively the same as what is currently approved in the 200 mg/5 mL (10 Day In-Use) product.*"³ The RLD is identified as EryPed® (Erythromycin Ethylsuccinate for Oral Suspension, USP), 400 mg/5 mL & 200 mg/ 5 mL with In-Use shelf life of 35 days stored at room temperature in NDA 050207. NDA 050207 also includes E.E.S. Granules 200 mg/5 mL with In-Use shelf life of 10 days stored in the refrigerator, with which ANDA 062055 was originally found equivalent and approved in 1978.

4.1 Current or Draft Guidance

There is a draft product specific bioequivalence guidance for Erythromycin ethylsuccinate, Granule, oral, at the "Bioequivalence Recommendations for Specific Products" website:

2

(b) (4)

³ ANDA 062055, Cover Letter (SN0020:2018-05-25: PAS), Sequence 0020 (95) 05/25/2018 SUPPL-35 (Manufacturing (CMC))/Multiple Categories/Subcategories. <\\cdsesub1\evsprod\anda062055\0020\m1\us\cover-letter-signed.pdf>

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM506882.pdf>

4.2 Controls or Protocols

No controlled correspondence (CC) regarding excipients or formulation were identified during this review (search term “erythromycin ethylsuccinate” in FDA internal databases (e.g., <http://cdsogd1/Controls/Doc.Asp>, Mercado).

4.3 Orange Book Information

Erythromycin ethylsuccinate is currently available in both granule for oral suspension formulations (E.E.S. 200 mg/5 mL and Eryped 200 mg/5 mL Eryped 400 mg/5mL) and oral tablet formulations (E.E.S. 400 and erythromycin ethylsuccinate 400 mg tablets), as shown in Table 1 below.

Table 1: Orange Book Currently Approved Applications for Erythromycin Ethylsuccinate (n= 5)

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N050207		RLD	Erythromycin ethylsuccinate	Granule; oral	EQ 200 mg base/5 mL	E.E.S.	Arbor Pharmaceuticals LLC
N050207		RLD		Granule; oral	EQ 200 mg base/5 mL	EryPed	
N050207		RLD		Granule; oral	EQ 400 mg base/5 mL	EryPed	
A061905	BX			Tablet	EQ 400 mg base	E.E.S. 400	
A061904	BX			Tablet	EQ 400 mg base	Erythromycin Ethylsuccinate	

Source: Search on 08/21/2018 by this reviewer of the Orange Book,

https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

TE=Therapeutic Equivalence

RLD=Reference Listed Drug

4.4 RLD Formulation [NOT FOR FOIA]

The formulation of RLD, Arbor Pharmaceuticals LLC’s EryPed® (erythromycin ethylsuccinate for oral suspension) Oral Granules, 200 mg/5 mL and 400 mg/5 mL (NDA 050207), was obtained from NDA 050207, Module 3.2.P.1 Description and Composition of EryPed 200 (submitted in Sequence 0002 (111) 05/28/2010).

E.E.S.®, Eryped® 200, and Eryped® 400 are products consisting of a ^{(b)(4)} mixture of erythromycin ethylsuccinate with flavor, ^{(b)(4)} and other ingredients. These products are designed to be reconstituted with water as directed in the labeling when dispensed, resulting in a viscous liquid suspension for oral ingestion.

After reconstitution, each 5-mL teaspoonful of E.E.S.® (erythromycin ethylsuccinate for oral suspension, USP) reconstituted suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin; the reconstituted suspension is intended for storage in the refrigerator and use within 10 days. The inactive ingredients include: Citric acid, FD&C Red No. 3, magnesium aluminum silicate, sodium carboxymethylcellulose, sodium citrate, sucrose and artificial flavor.

Table 2: RLD Formulation of E.E.S Granules

Item Name	Amount/5 mL of Reconstituted Suspension	
	EES® Granules	
Erythromycin Ethylsuccinate, USP, (b) (4)	(b) (4)	
Sucrose, NF		
Acid, Citric, USP/EP, (b) (4)		
Sodium Carboxymethylcellulose, USP, (b) (4)		
Magnesium Aluminum Silicate, (b) (4) NF		
Sodium Citrate, USP/EP, (b) (4)		
Dye, Red, FD&C No.3		
(b) (4)		
Flavor, (b) (4) Cherry (b) (4)		
Theoretical Weight of (b) Granules		

(b) (4)

Eryped® 200 (erythromycin ethylsuccinate for oral suspension, USP) when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 mL (teaspoonful) or 100 mg per 2.5 mL (dropperful). Eryped® 400 (erythromycin ethylsuccinate for oral suspension, USP) when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 mL (teaspoonful). The inactive ingredients for Eryped® 200 and Eryped® 400 include: caramel, polysorbate, sodium citrate, sucrose, xanthan gum and artificial flavors. After reconstitution, Eryped® 200 and Eryped® 400 must be stored at or below 77°F and used within 35 days. The Eryped formulations differ from the E.E.S. formulation by (b) (4)

(b) (4)

Table 2: Eryped 200® and Eryped 400® Formulations

Item Name	Amount/5 mL of Reconstituted Suspension	
	Eryped® 200	Eryped® 400 (RLD)
Polysorbate (b) (4) NF	(b) (4)	
Caramel, NF, (b) (4)		
Erythromycin Ethylsuccinate, USP, (b) (4)		
Sucrose, NF (b) (4)		
Sodium Citrate, USP/EP, (b) (4)		
Xanthan Gum NF		
(b) (4)		
Flavor, (b) (4) Artificial (b) (4)		
(b) (4)		
(b) (4)		

Theoretical Weight	

(b) (4)

4.5 Proposed Generic Formulation

The formulation for the proposed two new strengths of erythromycin ethylsuccinate (EES) for oral suspension (OS), 200 mg/5 mL and 400 mg/5 mL (35 Day In-use), was obtained from Section 3.2.P.1 in the ANDA 062055 application submission dated 06/14/2018 [Sequence 0023 (98)].

As shown in Tables 4 and 5, while the proposed generic product contains (b) (4) methylparaben and (b) (4) polysorbate 80, (b) (4)

(b) (4) As shown in Table 6, compared to the previously approved strength of the generic erythromycin ethylsuccinate for oral suspension, 200 mg/5 mL (10 Day In-use), (b) (4)

(b) (4)

5 Labeling:

The current product label for EryPed® (erythromycin ethylsuccinate, USP), 200 mg/5 mL (Ery-Ped 200) and 400 mg/5 mL (Ery-Ped 400), was approved on 04/23/2018. Both products are granules, erythromycin ethylsuccinate for oral suspension, and intended primarily for pediatric use but can also be used in adults. After reconstitution, Ery-Ped 200 and Ery-Ped 400 must be stored at or below 77°F (25°C) and used within 35 days; refrigeration is not required. There is not a black box warning.

6 Discussion:

Questions from the Division of Bioequivalence II (DB II) of OGD in verbatim:

“Are there any safety concerns on the maximum daily intakes of Methylparaben and Polysorbate 80 in ANI Pharmaceuticals, Inc.’s Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL (35 Day In-Use) and Eq 400 mg base/5 mL (35 Day In-Use), based on the maximum daily dose and the context of use of this drug product?”

6.1 Applicant’s Justification

Although the proposed two new strengths of erythromycin ethylsuccinate, 200 mg/5 mL and 400 mg/5 mL (35 Day In-Use), contain (b) (4) methylparaben than its level in RLD and their own approved generic strength of 200 mg/5 mL (10 Day In-Use), the applicant did not provide any specific justification to support its use. Instead, in its cover letter to supplement-S035 submission, the applicant stated, *“The drug product formulations for the two new strengths, 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use), is qualitatively the same as what is*

currently approved in the 200 mg/5 mL (10 Day In-Use) product. There are no changes being proposed to the approved suppliers, specifications or controls for each of the inactive ingredients that are currently filed to this ANDA. Therefore, there are no respective documentation filed in Module 3.2.P.4.”

(b) (4)



7 Conclusion:

The proposed levels of methylparaben (b) (4) and polysorbate 80 (b) (4) in the current generic erythromycin ethylsuccinate oral suspension are acceptable from both Clinical and P/T perspectives.



Xin
Fu

Digitally signed by Xin Fu
Date: 9/09/2018 11:38:23AM
GUID: 5a4fe02d0023440835f92b7bce02d2c2



Sruthi
King

Digitally signed by Sruthi King
Date: 9/09/2018 04:08:46PM
GUID: 502d1b1300002b0559e552d5f6aa4cc2



Sarah
Yim

Digitally signed by Sarah Yim
Date: 9/09/2018 06:16:09PM
GUID: 50841a8900009e1fe2b0e31699e4e531

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 62055/S-035

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



ANDA 062055/S-035

**REQUEST FOR RECONSIDERATION
REQUEST DENIED**

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623
Attention: Ellen Camos
Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your supplemental abbreviated new drug application (sANDA), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL.

We also refer to your correspondence received on October 10, 2018, requesting reconsideration concerning the major classification.

CAPT Aaron W. Sigler has delegated your request for reconsideration to me, LCDR Andrew Kim, Supervisory Project Manager of the Division of Project Management.

I have carefully reviewed the materials you submitted in support of your request, as well as all other materials referenced herein.

I have completed my review of your request for reconsideration and deny your request for the following reasons.

FDA considers your request for reconsideration moot, as the matter under reconsideration is no longer applicable because the Agency approved ANDA 062055/S-035 on November 2, 2018. Consequently, I am denying your reconsideration request.

If you have any questions, call Surjit Basi, Regulatory Project Manager at (240) 402 - 8892.

Sincerely,

{See appended electronic signature page}

Andrew Kim, PharmD
LCDR, USPHS
Supervisory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research



Andrew
Kim

Digitally signed by Andrew Kim

Date: 11/06/2018 03:51:50PM

GUID: 508da70600028aaa57d6fc4456bcd799

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 02
Document Status: DRAFT		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Approval Type: FULL APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH)

RPM: Surjit Basi Team Leader: Kevin Herkenham

PI PII PIII PIV (eligible for 180 day exclusivity) Yes No MOU RX or OTC

ANDA #: 062055/S-035 Applicant: ANI Pharmaceuticals, Inc.

Established Product Name: Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL

Basis of Submission (RLD): Ery-Ped/NDA50207/ArborPharmaceuticals

Basis Of Submission Discontinued? Yes No

If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?

Yes FR Notice dated _____; Document Citation _____; FR. _____ (Example: 78 FR 67365)

No Consult completed but not yet published in FR

(Is ANDA based on an approved Suitability Petition? Yes No, if yes, use SP language in template)

Does the ANDA contain REMS? Yes No (If YES, initiate approval action 6 weeks prior to target action date)

Regulatory Project Manager Evaluation:

Date: 10/25/2018

Date (Received) Acceptable for Filing -- Date 5/25/2018

Date last Complete Response (CR) letter was issued -- Date _____

Previously reviewed and tentatively approved (if applicable) --- Date _____

YES	NO			
<input checked="" type="checkbox"/>	<input type="checkbox"/>	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)		
		<table border="0"> <tr> <td style="vertical-align: top;"> Date of Acceptable Bioequivalence <u>9/14/2018</u> <ul style="list-style-type: none"> Date of BE Guidance (if any) <u>6/2016</u> Date of Acceptable Labeling <u>6/29/2018</u> <ul style="list-style-type: none"> Date of last RLD labeling update <u>4/23/2018</u> Date of Acceptable Quality <u>10/24/2018</u> <ul style="list-style-type: none"> DMF No(s). (b) (4) Date(s) Acceptable <u>10/19/18</u> No outstanding DMF review amendments <input checked="" type="checkbox"/> Date of Acceptable Overall Manufacturing Inspection <u>10/10/2018</u> </td> <td style="vertical-align: top;"> If applicable: Date of Acceptable Microbiology _____ Date of Acceptable Clinical Review _____ Date of Acceptable Dissolution _____ Date of Acceptable REMS _____ </td> </tr> </table>	Date of Acceptable Bioequivalence <u>9/14/2018</u> <ul style="list-style-type: none"> Date of BE Guidance (if any) <u>6/2016</u> Date of Acceptable Labeling <u>6/29/2018</u> <ul style="list-style-type: none"> Date of last RLD labeling update <u>4/23/2018</u> Date of Acceptable Quality <u>10/24/2018</u> <ul style="list-style-type: none"> DMF No(s). (b) (4) Date(s) Acceptable <u>10/19/18</u> No outstanding DMF review amendments <input checked="" type="checkbox"/> Date of Acceptable Overall Manufacturing Inspection <u>10/10/2018</u> 	If applicable: Date of Acceptable Microbiology _____ Date of Acceptable Clinical Review _____ Date of Acceptable Dissolution _____ Date of Acceptable REMS _____
Date of Acceptable Bioequivalence <u>9/14/2018</u> <ul style="list-style-type: none"> Date of BE Guidance (if any) <u>6/2016</u> Date of Acceptable Labeling <u>6/29/2018</u> <ul style="list-style-type: none"> Date of last RLD labeling update <u>4/23/2018</u> Date of Acceptable Quality <u>10/24/2018</u> <ul style="list-style-type: none"> DMF No(s). (b) (4) Date(s) Acceptable <u>10/19/18</u> No outstanding DMF review amendments <input checked="" type="checkbox"/> Date of Acceptable Overall Manufacturing Inspection <u>10/10/2018</u> 	If applicable: Date of Acceptable Microbiology _____ Date of Acceptable Clinical Review _____ Date of Acceptable Dissolution _____ Date of Acceptable REMS _____			
<input checked="" type="checkbox"/>	<input type="checkbox"/>	MMA: All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d).		
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Are consults pending for any discipline?		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable - Decline to inspect		
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? If YES → OGD Policy Lead confirmed ANDA may proceed <input type="checkbox"/> ; Memo uploaded (if applicable) <input type="checkbox"/>		
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES → Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews <input type="checkbox"/>		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed <u>10/22/2018</u>		
Review Discipline/Division and RPM TL Endorsements				
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Applicable review discipline/division endorsements completed		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	RPM Team Leader endorsement completed		
Additional Notes (if applicable)				

Lead Division: Program Management

Effective Date:

Page 1 of 7

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:

OGD Approved Controlled Documents SharePoint

<http://sharepoint.fda.gov/orgs/CDER-OGD/SitePages/OGD%20Document%20Control.aspx>

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 10/26/2018

Name: MHS

<p>Patent/Exclusivity Certification: <input checked="" type="checkbox"/> PI <input type="checkbox"/> PII <input type="checkbox"/> PIII <input type="checkbox"/> PIV <input type="checkbox"/> section viii If Paragraph IV Certification- did applicant: Notify patent holder/NDA holder: Yes <input type="checkbox"/> No <input type="checkbox"/> Was applicant sued w/in 45 days: Yes <input type="checkbox"/> No <input type="checkbox"/> Has case been settled: Yes <input type="checkbox"/> No <input type="checkbox"/> Applicant addressed all listed exclusivities Yes <input type="checkbox"/> No <input type="checkbox"/> Do the patent and exclusivity certifications align? Yes <input type="checkbox"/> No <input type="checkbox"/> Have there been any revisions to the use code since the original submission? Yes <input type="checkbox"/> No <input type="checkbox"/></p>	<p>RLD = <u>Eryped</u> NDA# <u>50207</u> <input checked="" type="checkbox"/> RX or <input type="checkbox"/> OTC Date Checked in Orange Book#: <u>10/26/2018</u> Type of Letter: <input checked="" type="checkbox"/> APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH) LETTER RECOMMENDED FOR DRUGS@FDA Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p>
<p>Forfeiture Information Is a forfeiture memo needed for the first applicant: Yes <input type="checkbox"/> No <input type="checkbox"/> If yes, the date forfeiture memo was completed Date _____ ANDA # _____</p>	<p>180 Day Exclusivity Information Is applicant eligible for 180 day exclusivity Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> <input type="checkbox"/> Sole <input type="checkbox"/> Shared ANDA Exclusivity for each strength: Yes <input type="checkbox"/> No <input type="checkbox"/> Which strength(s) eligible _____</p>
<p>Comments: S 035 submitted on May 25, 2018 for inclusion of 200 mg/5 mL and 400 mg/5 mL with equivalence to Eryped. It is noted for the record that NDA 50207 is marketed under both the E.E.S(10 Day In-Use) and Eryped(35 Day In-use) proprietary names, thus this applicant is able to seek the additional TE rating because the RLD is marketed under a single NDA. There are no unexpired patents or exclusivities that protect NDA 50207. Therefore, this sANDA is eligible for immediate Final AP from a patent/legal perspective.</p>	
<p>180 Day Exclusivity Status/Landscape: N/A Citizen Petitions Impact: N/A First Legally Approvable Date: N/A If Tentative Approval, anticipated full approval date: N/A</p>	

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 02
Document Status: DRAFT		
Title: Approval Routing Summary Form		Author: Heather Strandberg

2. **Final Decision**

Date: **11/2/2018**

Name: **PCS**

ANDA received on **5/25/2018** for the **200 mg/5 mL and 400 mg/5 mL** strengths

RTR'd? Yes No If yes, RTR'd on Enter date

Priority Status? Yes No If yes, prioritization factor is **first generic for the 400 mg/5 mL**

Basis of Submission (RLD)

Drug Name **Ery-Ped**
 NDA # **050207**
 Applicant Name **Arbor Pharmaceuticals, LLC**

Verified the following:

1. Completion of the following endorsement tasks, if applicable:
 - a. Division of Legal and Regulatory Support Endorsement
 - b. Paragraph IV Evaluation
 - c. REMS Endorsement
 - d. Quality Endorsement
 - e. Bioequivalence Endorsement
 - f. Clinical-Bioequivalence Endorsement
 - g. Labeling Endorsement
 - h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates at Drugs@FDA since the Labeling Endorsement
5. No issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments since Quality Endorsement
9. No amendments received since the RPM Team Leader Endorsement

This ANDA is ready for **FULL APPROVAL**.

Lead Division: Program Management	Effective Date:	Page 3 of 7
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Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:

OGD Approved Controlled Documents SharePoint

<http://sharepoint.fda.gov/orgs/CDER-OGD/SitePages/OGD%20Document%20Control.aspx>

Following this page, 3 Pages Withheld in Full as (b)(4)

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 02
Document Status: DRAFT		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02		Kevin Denny	Reviser	<ul style="list-style-type: none"> • Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 • Remove content adequately captured in the platform • Update information captured in the Division of Legal and Regulatory Support Endorsement section • Other minor administrative corrections to format and content

Lead Division: Program Management	Effective Date:	Page 7 of 7
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Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:
 OGD Approved Controlled Documents SharePoint
<http://sharepoint.fda.gov/orgs/CDER-OGD/SitePages/OGD%20Document%20Control.aspx>



ANDA 062055/S-035

**REQUEST FOR RECONSIDERATION
ACKNOWLEDGEMENT**

ANI Pharmaceuticals Inc.
210 Main Street West
Baudette, MN 56623
Attention: Ellen Camos
Vice President of Regulatory Affairs

Dear Madam:

This is in reference to your supplemental abbreviated new drug application (sANDA), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL.

We acknowledge your correspondence received on October 10, 2018, requesting reconsideration concerning the major classification. Your request has been forwarded for review to LCDR Andrew Kim, Acting Deputy Director, Division of Project Management.

Your request for a teleconference is granted and the teleconference is scheduled as follows:

Date: October 26, 2018
Time: 1:15 PM to 1:45 PM (EST)

Phone Arrangements

Call In Number: 1-877-465-7975 (US Toll Free)
Meeting Number: 902 857 826

CDER Participants:

Yajun Tu, OPQ, OPRO
Ankara Yokum, OPQ, OPRO
Vidya Pai, OPQ, OPF
Thuy-Thanh Nguyen, OPQ, OPF
Melissa Furness, OPQ, OPPQ
Laurie Graham, OPQ, OPPQ
Kevin Herkenham, OGD, DPM
Andrew Kim, OGD, DPM
Anh Pham, OGD, DPM
Surjit Basi, OGD, DPM
Lisa Oh, OGD, DPM

The GDUFA goal date for providing our written response is November 8, 2018.

If you have any questions, contact Surjit Basi, Regulatory Project Manager at (240) 402 - 8892.

Sincerely,

{See appended electronic signature page}

Surjit Basi
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research



Surjit
Basi

Digitally signed by Surjit Basi
Date: 10/24/2018 08:59:13AM
GUID: 525e90ae0003b4d0a4d4b1824807db1d



ANDA 062055/S-035

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623
Attention: Ellen Camos
Vice President of Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on September 27, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major supplement amendment, the GDUFA goal date for review of this priority major supplement amendment is January 26, 2019. If FDA determines that an inspection is required to validate the information contained in this priority major supplement amendment and a Pre-Submission Facility Correspondence (PFC) was not submitted or not accepted, the GDUFA goal date for review of this priority major supplement amendment is July 26, 2019.

If you have any questions, contact Surjit Basi, Regulatory Project Manager, at (240) 402 - 8892.

Sincerely,

{See appended electronic signature page}

Surjit Basi
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Surjit
Basi

Digitally signed by Surjit Basi

Date: 10/03/2018 02:56:22PM

GUID: 525e90ae0003b4d0a4d4b1824807db1d



ANDA 062055/S-035

**INFORMATION REQUEST
PRIOR APPROVAL SUPPLEMENT**

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623

Attention: Ellen Camos
Vice President of Regulatory Affairs

Dear Madam:

This is in reference to your supplemental abbreviated new drug application (sANDA) received for review on May 25, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL.

1. Please note that there is a manufacturing facility (critical intermediate) that is included in a DMF referenced by DMF (b) (4) for Erythromycin Ethylsuccinate that was not included on your form 356h. Please contact your DMF holder to resolve any discrepancies and clarify which DMF related facilities support your application. Please note that a revised 356h form will be required to add any new facilities to your application.
2. DMF# (b) (4) for Erythromycin Ethylsuccinate is being reviewed and the DMF holder, (b) (4) will be notified of any deficiencies. We will work with the DMF holder to resolve any issues if the DMF holder responds in a timely manner. Please be aware that the quality review of the ANDA cannot be fully completed until all DMF deficiencies are adequately resolved. Therefore, additional ANDA deficiency comments may be issued based on the outcome of the DMF review. Please acknowledge this in your response.
3. (b) (4)
4. Please submit updated stability data from accelerated and long-term stability studies as data becomes available.

Provide a complete response to these deficiencies by September 28, 2018. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted.

Send your submission through the Electronic Submission Gateway <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
PRODUCT QUALITY**

If you do not submit a complete response by September 28, 2018, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, *ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA* available on FDA's website.

Secure email between CDER and sponsors is 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 the 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

If you have any questions, please contact Yajun Jason Tu, Regulatory Business Process Manager, at yajun.tu@fda.hhs.gov or 240-402-4202.

Sincerely,

{See appended electronic signature page}

Yajun Jason Tu, PharmD, PhD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Yajun (Jason)
Tu

Digitally signed by Yajun (Jason) Tu

Date: 9/18/2018 03:09:29PM

GUID: 531537c500005490fbb77d7b953b81b5



ANDA 62055/S-035

**DENIAL—
COMPETITIVE GENERIC THERAPY DESIGNATION**

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623
Attention: Ellen Camos
Vice President of Regulatory Affairs

Dear Madame:

This letter is in reference to your abbreviated new drug application (ANDA) for Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL, received on July 28, 1977 and approved on November 27, 1978.

You submitted a supplement to this ANDA, dated May 25, 2018. We acknowledge that you requested concurrently with supplement 035 submitted on May 25, 2018, that the drug product under your ANDA be designated as a Competitive Generic Therapy (CGT) pursuant to section 506H(b) of the Federal Food Drug & Cosmetic Act.

We have reviewed your request and have determined, consistent with section 506H(b)(2) of the FD&C Act, that the drug product under your ANDA does not qualify for designation as a CGT because your request was made after the submission of your original ANDA, and thus was not made concurrently with or at any time prior to the submission of your ANDA 62055.

If you have concerns regarding the content of this letter, you should contact the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov¹.

Sincerely,

Rinku Patel

-S4

Digitally signed by Rinku Patel -S4
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rinku Patel -S4,
0.9.2342.19200300.100.1.1=2000401187
Date: 2018.07.24 16:57:31 -04'00'

For Martin Shimer, R.Ph.
Deputy Director
Division of Legal and Regulatory Support
Office of Generic Drug Policy
Office of Generic Drugs
Center for Drug Evaluation and Research

¹ A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

Considering the above information, please provide your input on the following question:

- 1. Are there any safety concerns on the maximum daily intakes of Methylparaben and Polysorbate 80 in ANI Pharmaceuticals, Inc.'s Erythromycin Ethylsuccinate for Oral Suspension USP, Eq 200 mg base/5 mL (35 Day In-Use) and Eq 400 mg base/5 mL (35 Day In-Use), based on the maximum daily dose and the context of use of this drug product?**

Thank you for your consideration. Please address your consult regarding the above issue to ethan.stier@fda.hhs.gov.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Attachment

The RLD formulation



2024647 N050207
Erythromycin Ethylsuc



ANDA 062055/S-035

**ACKNOWLEDGEMENT
sANDA RECEIPT**

ANI Pharmaceuticals, Inc.
210 Main Street West
Baudette, MN 56623
Attention: Ellen Camos

Dear Ellen Camos:

This is in reference to your supplemental abbreviated new drug application (sANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA or the Agency) has made a threshold determination that this sANDA is substantially complete. This sANDA is received for review.

NAME OF DRUG: Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL

DATE OF APPLICATION: May 25, 2018

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: May 25, 2018

Reference is made to the information requests dated June 8 and 18, 2018 and to any amendments thereafter.

This supplement is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). Your request for a priority review of this submission meets the criteria listed in section 505(j)(11)(A) of the FD&C Act or the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority supplement, the GDUFA goal date for review of this priority supplement is September 24, 2018. If FDA determines that an inspection is required to validate the information contained in this priority supplement and a Pre-Submission Facility Correspondence was not submitted or was found ineligible for further assessment, the GDUFA goal date for review of this priority supplement is March 24, 2019.

For more information, please refer to the guidance for industry *ANDA Submissions – Prior Approval Supplements Under GDUFA* available on FDA's website.¹

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Kevin Herkenham, Project Manager Team Leader, at Kevin.Herkenham@FDA.HHS.GOV² or 240-402-8964. We also recommend that you sign up for Generic Drug e-mail updates,³ which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Ilinca Duveau, Pharm.D.
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

¹We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

²A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

³<http://go.fda.gov/subscriptionmanagement>



Ilinca
Duveau

Digitally signed by Ilinca Duveau

Date: 6/20/2018 03:11:10PM

GUID: 53b44d7d000131fd11df4744f93d2705

ANDA FILING CHECKLIST

(Post June 20, 2014)

ANDA: **062055-Supp-35**

APPLICANT: **ANI Pharmaceuticals, Inc.**

RELATED APPLICATION(S): Related applications

DRUG PRODUCT NAME: **Erythromycin Ethylsuccinate for Oral Suspension USP**

STRENGTH(S): **400 mg/5 mL & 200 mg/5 mL**

LETTER (356h) DATE: **May 25, 2018**

RECEIVED DATE: **May 25, 2018**

GDUFA GOAL DATE: **September 24, 2018** *Goal date may have changed. Refer to the platform for most up-to-date goal date.*

Type II DRUG MASTER FILE #: (b) (4)

BASIS OF SUBMISSION:

(If reference standard is an ANDA, complete right column)

Reference listed drug (RLD): **E.E.S./EryPED**

Reference standard: RS

New drug application (NDA) number: **050207**

NDA/ANDA number: NDA/ANDA number

NDA holder: **Arbor Pharmaceuticals LLC**

NDA/ANDA holder: NDA/ANDA holder

Drug product: **Erythromycin Ethylsuccinate
for Oral Suspension USP**

Drug product: Drug product

Completion Signature

6/20/2018

X Jing Shao

Filing Reviewer

Signed by: Jing Shao -S

Recommendation:

FILE REFUSE to RECEIVE

- Confirm that appropriate Application Specific Inspection Criteria have been checked
- QC Application Information Task Completed (Update Product Information, Patent and Policy in Project and Program Level) *(any corrections should be sent to CDERInformatics)*
- GDUFA Obligations Met (Filing Fee, Type II DMF Fee, and Facility Fee) - (internal notation-if not met contact: cder-gdufa-applications@fda.hhs.gov)
- ~~PFC: 60 days prior to ANDA submission Signed certification statement indicating information is unchanged~~
- DMF Complete Assessment (N/A)
- Policy Alert List ANDA – check for updates prior to issuing IR/action letter
- This is a combination product as defined under 21 CFR 3 (e.g., drug/device, drug/biologic) - **does not come with a measuring cup; therefore, not a combination product**
- Competitive Generic Therapy at the time of filing. Notify PET team through platform (tag: Rinku Patela and Iain Margand) (Request CGT)
- All documents submitted in eCTD Format (see next page)

- a. No security settings
- b. Fonts embedded or standard fonts used
- c. Font sizes ranging from 9 to 12 point (including scanned images)
- d. Correct page orientation
- e. Scanned documents are text searchable
- f. Easily legible
- g. Adequate bookmarks (if > 5 pages)
- h. Descriptive bookmarks
- i. Bookmarks set to inherit zoom
- j. Hyperlinks (especially if there's a Table of Contents; > 5 pages)
- k. Hyperlinks set to inherit zoom
- l. Hyperlinks open in a new window
- m. Navigation tab open to Bookmarks Panel and Page (unless there are no bookmarks)
- n. Page Layout and Magnification set to Default
- o. Descriptive Leaf Titles

DEVIATIONS FROM GUIDANCE RECOMMENDATIONS:

Note any deviations within the ANDA submission affecting BE/OPQ review:

In module 5.2, file "Erythromycin Ethylsuccinate for Oral Suspension BE Companion Document", the applicant provides justification on why analytical studies and data was not provided on both analytes per the PSG and that this is considered a technical review based on the applicant's statement.

ADDITIONAL COMMENTS: All deficiencies were resolved in seq 0023 and seq0024

Applicant contact information (U.S. Agent information)

30. Typed Name and Title of Applicant's Responsible Official Ellen Camos, Vice President of Regulatory Affairs		31. Date (mm/dd/yyyy) 05/25/2018
32. Telephone Number (Include country code if applicable and area code) (b) (6)	33. FAX Number (Include country code if applicable and area code) 888.519.0459	34. Email Address ellen.camos@anipharmaceuticals.com
35. Address of Applicant's Responsible Official		
Address 1 (Street address, P.O. box, company name c/o) 210 Main Street West		
Address 2 (Apartment, suite, unit, building, floor, etc.)		
City Baudette	State/Province/Region MN	
Country USA	ZIP or Postal Code 56623	

Copy and Paste the following Screen shots:

From: Gaines, Tangela
Sent: Monday, June 18, 2018 12:03 PM
To: ellen.camos@anipharmaceuticals.com
Cc: ANDAFiling <ANDAFiling@fda.hhs.gov>
Subject: ANDA 062055/S-35 Filing Review Comments

Dear Ellen Camos:

This electronic mail is in reference to ANDA 062055-Supplement-35 submitted on May 25, 2018 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

SPECIAL INSTRUCTIONS:

- We request that you acknowledge the receipt of this email correspondence.
- Provide a complete response to all of the items identified below **within 7 calendar days** from the date of this communication. **Response due by 6/25/2018; responded on 6/19/2018**
- If a complete response is not submitted to the ANDA and received within 7 calendar days, the application will be deemed incomplete and will be refused for receipt.
- Your response should contain a point-by-point reply to each of the identified comment(s) with corresponding hyperlink(s), where applicable, to the body of data within the ANDA.
- You should notify me via email or telephone when you have submitted your response.
- Your cover letter should clearly indicate **Filing – Response to Information Request**.
- Any questions or need for clarification with respect to any of the following deficiencies can be sent to me, the project manager assigned to this ANDA during filing review. A teleconference may be requested within 1 business day of this email. With your request, you must clearly identify your question(s). **(Note: The teleconference will be limited to a discussion of only the questions provided in your teleconference request. Also, your query does not place a hold on the timeframe in which the response must be submitted, as per bullet 2.)**

1. Correct the following on Form FDA 356h:

- Revise Field 13 to include all proposed strengths. **Resolved in seq0024**

Note: Provide a fillable PDF copy of the 356h in all your submissions if you are submitting a scanned signed copy of the 356h, otherwise the omission of the fillable PDF copy of the 356h will be counted as a deficiency.

Best Regards,

LT Tangela Gaines, PA-C
Unites States Public Health Service
Project Manager-Division of Filing Review
FDA/CDER/OGD/ORO/DFR
10903 New Hampshire Avenue, Bldg. 75
Silver Spring, MD 20993
Tangela.Gaines@fda.hhs.gov



Correspondence(s), if applicable, (should include a screenshot of the Outlook email including the date)

From: Gaines, Tangela
Sent: Friday, June 08, 2018 2:02 PM
To: ellen.campos@anipharmaceuticals.com
Cc: ANDAFiling <ANDA.Filing@fda.hhs.gov>
Subject: ANDA 062055/S-35 Filing Review Comments

Dear Ellen Camos:

This electronic mail is in reference to ANDA 062055/S-35 submitted on May 25, 2018 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

SPECIAL INSTRUCTIONS:

- We request that you acknowledge the receipt of this email correspondence.
- Provide a complete response to all of the items identified below **within 7 calendar days** from the date of this communication. **Response due by 6/15/2018; responded on 6/14/2018.**

- b. Per the guidance for industry entitled, *M2 eCTD: Electronic Common Technical Document Specification* located on the internet, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073240.pdf>, module 2.7.1 and 2.7.4 “should consist of a single file” (MS Word and PDF format) rather than providing individual tables as separate documents. In addition, the tables should follow the most current model bioequivalence tables. **Resolved in seq0023**
3. Provide a samples-statement of availability and identification in module 3.2.S.4.3. **Resolved in seq0023**
4. We note that you provided the “Drug Product Formulation” after reconstitution. (b) (4)
(b) (4)
(b) (4)
5. In module 3.2.R, provide the Executed Batch Reconciliation tables to include theoretical, actual, and packaged yield. Theoretical, actual, and packaged yield should also be expressed in units of measure (i.e. number of bottles). **Resolved in seq0023**
6. In module 3.2.P.8.3, provide the withdrawal (pull) dates for each time point for your long-term stability studies (including all batches, conditions, and packaging configurations) in both the “Stability Data” file and the individual data tables. **Resolved in seq0023**

Additional Comment:

The study title listed in Table 3 (Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE Studies) does not match its respective study number. Please revise accordingly. **Resolved in seq0023**

Note: Provide a fillable PDF copy of the 356h in all your submissions if you are submitting a scanned signed copy of the 356h, otherwise the omission of the fillable PDF copy of the 356h will be counted as a deficiency.

Best Regards,

LT Tangela Gaines, PA-C
Unites States Public Health Service
Project Manager-Division of Filing Review
FDA/CDER/OGD/ORO/DFR
10903 New Hampshire Avenue, Bldg. 75
Silver Spring, MD 20993
Tangela.Gaines@fda.hhs.gov



THIS ELECTRONIC DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please

GDUFA Obligations Met

Draft Guidance on Erythromycin Ethylsuccinate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Erythromycin ethylsuccinate

Dosage Form; Route: Granule; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover *in vivo*
Strength: EQ 400 mg Base/5 mL
Subjects: Healthy males and females (non-pregnant and non-lactating), general population
Additional comments: Females should not be pregnant or lactating, and, if applicable, should practice abstinence or contraception during the study.
2. Type of study: Fed
Design: Single-dose, two-way crossover *in vivo*
Strength: EQ 400 mg Base/5 mL
Subjects: Healthy males and females (non-pregnant and non-lactating), general population
Additional comments: See comments above.

Analytes to measure (in appropriate biological fluid): Erythromycin (free base and total) in plasma

Bioequivalence based on (90% CI): Erythromycin

Waiver request of in vivo testing: Eryped[®] 200, EQ 200 mg Base/5 mL, and E.E.S.[®] 200, EQ 200 mg Base/5 mL based on (i) acceptable bioequivalence studies on the Eryped[®] 400, EQ 400 mg Base/5 mL, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended **Dissolution Methods** Web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

N/A PEPFAR NCE-1 Wavier of Exclusivity

Receipt date of ANDA submission after the approval date per Orange Book

Acceptable

Copy and Paste Orange Book screen shots (ensure that all patents are addressed for each proposed strength)

Search Results for Proprietary Name, Active Ingredient or Application Number: 050207

3 records returned

RX OTC DISCN

CSV Excel

Display 50 records per page

Search for text in the table:

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ERYTHROMYCIN ETHYLSUCCINATE	E.E.S.	N050207	GRANULE	ORAL	EQ 200MG BASE/5ML		RLD		ARBOR PHARMACEUTICALS LLC
RX	ERYTHROMYCIN ETHYLSUCCINATE	ERYPED	N050207	GRANULE	ORAL	EQ 200MG BASE/5ML		RLD		ARBOR PHARMACEUTICALS LLC
RX	ERYTHROMYCIN ETHYLSUCCINATE	ERYPED	N050207	GRANULE	ORAL	EQ 400MG BASE/5ML		RLD	RS	ARBOR PHARMACEUTICALS LLC

ERYPED (ERYTHROMYCIN ETHYLSUCCINATE)
EQ 200MG BASE/5ML

Active Ingredient: ERYTHROMYCIN ETHYLSUCCINATE

Proprietary Name: ERYPED

Dosage Form; Route of Administration: GRANULE; ORAL

Strength: EQ 200MG BASE/5ML

Reference Listed Drug: Yes

Reference Standard: No

TE Code:

Application Number: N050207

Product Number: 003

Approval Date: Mar 30, 1987

Applicant Holder Full Name: ARBOR PHARMACEUTICALS LLC

Marketing Status: Prescription

[Patent and Exclusivity Information](#)

ERYPED (ERYTHROMYCIN ETHYLSUCCINATE)
EQ 400MG BASE/5ML

Active Ingredient: ERYTHROMYCIN ETHYLSUCCINATE
Proprietary Name: ERYPED
Dosage Form; Route of Administration: GRANULE; ORAL
Strength: EQ 400MG BASE/5ML
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N050207
Product Number: 002
Approval Date: Approved Prior to Jan 1, 1982
Applicant Holder Full Name: ARBOR PHARMACEUTICALS LLC
Marketing Status: Prescription
[Patent and Exclusivity Information](#)

Patent and Exclusivity for: N050207

Product 003
ERYTHROMYCIN ETHYLSUCCINATE (ERYPED) GRANULE EQ 200MG BASE/5ML

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code
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There are no unexpired patents for this product in the Orange Book database.

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
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There is no unexpired exclusivity for this product in the Orange Book database.

1.4	1.4.2	<p>Statement of right of references 21 CFR §314.50(g)(1) DMF Written Statement of authorization for reference (copy of letter of authorization (LoA) received from DMF holders)</p> <p>N/A 1. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient (API) 2. Type II DMF# Enter Type II DMF #</p> <p>N/A 3. Type III DMF authorization letter(s) for container closure</p>
		<p>Drug Master Files (DMF) Letters of Authorization All cross referenced DMFs in association with this PAS submission have previously been referenced within this ANDA. This includes all currently referenced Type II (drug substance) and Type III (Container Closure) DMFs. Therefore, no Letters of Authorization are required to be submitted in Module 1.4.1 for this PAS.</p>
1.12	1.12.4	<p>N/A Request for comments and advice – Proprietary name requested If Yes, did the applicant provide the request as a separate electronic amendment labeled “Proprietary Name Request” at initial time of filing</p> <p>N/A 1. Yes 2. No – contact the applicant to submit the request as a separate electronic amendment</p>

		Comments
1.12.11		<p>Basis for submission 21 CFR §314.94(a)(3) Applicant identifies the following:</p> <p>YES 1. RLD application # YES 2. RLD drug product YES 3. RLD Holder N/A 4. RS (if different from the RLD) N/A 5. RS # (if applicable)</p> <p>ANDA suitability petition required? 21 CFR §10.20 21 CFR §10.30 21 CFR §314.93 N/A If Yes, assigned docket number Docket number Copy of FDA’s correspondence approving the petition (21 CFR §314.94(a)(3)(iii))</p> <p>ANDA Citizen’s Petition required? 21 CFR §10.25(a) 21 CFR §10.30 21 CFR §314.122 N/A If Yes, Petition number Petition number Copy of petition</p> <p>Acceptable</p>
1.12.12		<p>Comparison between generic drug and RLD 505(j)(2)(A) 21 CFR §314.94(a)(4) to (6)</p> <p>SAME AS RLD 1. Condition(s) of use SAME AS RLD 2. Active ingredient(s) JUSTIFIED 3. Inactive ingredient(s) SAME AS RLD 4. Route of administration(s) SAME AS RLD 5. Dosage form SAME AS RLD 6. Strength(s)</p> <p>Acceptable</p>
1.12.14		<p>Environmental analysis from applicant 21 CFR 25.15(d) 21 CFR 25.20 21 CFR 25.22 21 CFR 25.30 or 25.31</p> <p>Select Environmental assessment (EA) Select If applicable, environmental impact statement (EIS) Select Claim of categorical exclusion Select Statement: “to the applicant’s best of knowledge no extraordinary circumstances exist”</p> <p>Comments</p>
1.12.15		<p>Request for waiver 21 CFR 320.22 320.24(b)(6) YES Request for waiver of in vivo BA/BE Study(ies)</p> <p>Acceptable</p>
1.14	1.14.1	<p>Draft labeling 21 CFR 314.94(a)(8)(ii) and (iv) (if applicant provides “Final Labeling,” the labeling information should be provided in Module 1.14.2.)</p> <p>1.14.1.1 Draft carton and container labels YES Electronic copy (each strength and container) -OR-</p> <p>1.14.1.2 Annotated draft labeling text YES Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated</p> <p>1.14.1.3 Draft labeling text (does not apply to OTC products) YES 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically</p> <p>1.14.1.4 Labeling comprehension studies N/A Refer to Pharmacy Bulk Package (PBP) Sterility Assurance Table (for PBP’s only) See link below for table: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf</p> <p>Acceptable</p>
	1.14.3	<p>Listed drug labeling</p> <p>1.14.3.1 Annotated comparison with listed drug 21 CFR §314.94(a)(8)(iv) YES Side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated</p> <p>a. Container closure system (if different from what is approved for the RLD) N/A i. Vial or ampule vs. prefilled syringe N/A ii. Vial vs. ampule</p>

	N/A b. Drug product packaged in an IV bag
Select	1.14.3.3 Labeling text for reference listed drug 21 CFR §314.94(a)(8)(iv)
Select	RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label
	Acceptable

Copy and Paste Side by Side Comparison of the "How Supplied" section from the Package Insert



(b) (4)

MODULE 2: CTD SUMMARIES

2.3 QUALITY OVERALL SUMMARY (QOS)

21 CFR 314.50(c)

2.3	<p>N/A E-Submission: PDF N/A MS Word</p> <p>Additional information regarding QbR may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm</p> <p>N/A Question based review (QbR)</p>														
	<p>N/A</p>														
	<p>N/A 2.3.S Drug substance (API)</p> <ul style="list-style-type: none">2.3.S.1 General information2.3.S.2 Manufacture2.3.S.3 Characterization2.3.S.4 Control of drug substance2.3.S.5 Reference standards2.3.S.6 Container closure system2.3.S.7 Stability														
	<p>N/A; no changes</p> <p>Drug Substance</p> <p>As previously stated, the drug substance manufacturer is the same as one of the current approved sources for this ANDA: (b) (4). The information on this drug substance supplier is provided below for ease of reference.</p> <table border="1"><thead><tr><th colspan="5">DMF REFERENCES (Type II)</th></tr><tr><th>No.</th><th>Holder</th><th>Manufacturing Address</th><th>US Agent</th><th>Facility ID No.</th></tr></thead><tbody><tr><td colspan="5" style="text-align: right;">(b) (4)</td></tr></tbody></table> <p>There are no changes being proposed to the drug substance in this PAS. As such, only the batch analysis for the lot of API used in the exhibit batch manufacturing and reference standards utilized in the testing of the API are being provided. Please refer to Module 3.2.S.4.4 and Module 3.2.S.5 for the associated documentation.</p>	DMF REFERENCES (Type II)					No.	Holder	Manufacturing Address	US Agent	Facility ID No.	(b) (4)			
DMF REFERENCES (Type II)															
No.	Holder	Manufacturing Address	US Agent	Facility ID No.											
(b) (4)															
<p>N/A 2.3.P Drug Product</p> <ul style="list-style-type: none">2.3.P.1 Description and composition of the drug product2.3.P.2 Pharmaceutical development<ul style="list-style-type: none">2.3.P.2.1 Components of the drug product<ul style="list-style-type: none">2.3.P.2.1.1 Drug substance (API)2.3.P.2.1.2 Excipients2.3.P.2.2 Drug Product oral solids: immediate release or modified release (matrix technology or compressed film coated components) tablet scoring data per guidance for industry, <i>Tablet Scoring: Nomenclature, Labeling and Data for Evaluation</i> (March 2013) (if applicable)2.3.P.2.3 Manufacturing process development2.3.P.2.4 Container closure system2.3.P.3 Manufacture2.3.P.4 Control of excipients															

- 2.3.P.5 Control of drug product
- 2.3.P.6 Reference standards and materials
- 2.3.P.7 Container closure system
- 2.3.P.8 Stability

In module 2.3, provide a Quality Overall Summary (in both MS Word and PDF format) for the drug product, that adheres to the Question-Based Review format. **Resolved in seq0023**

Drug Product Manufacturer and Contract Facilities

The new strengths for Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use) will be manufactured, packaged, and tested at ANI (DUNs: 148515737 / FEI: 2111358) located in Baudette, MN. ANI is a facility previously filed⁵ in this ANDA for manufacturing and testing of the 200 mg/5 mL (10 Day In-Use).

In this submission, ANI intends to initiate manufacturing, packaging, and testing of the new strengths, 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use), at this facility. ANI's most recent FDA inspection occurred May 15, 2017 – May 18, 2017, which was closed with a satisfactory conclusion. A copy of ANI's cGMP Certificate is located in Module 3.2.P.3.1.

DRUG PRODUCT			
Name	Address	Facility ID No.	Function/ Responsibility
ANI Pharmaceuticals , Inc.	210 Main Street West Baudette, MN 56623	FEI: 2111358	Drug Substance: Analytical Testing Drug Product: Manufacturing, Packaging, In-Process Analytical Testing, Final Dosage Form Release Analytical Testing, Stability Analytical Testing Excipients: Analytical Testing, Microbiological Testing
		DUNs: 148515737	

(b) (4)



Per the guidance for industry entitled, *M2 eCTD: Electronic Common Technical Document Specification* located on the internet, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073240.pdf>, module 2.7.1 and 2.7.4 “should consist of a single file” (MS Word and PDF format) rather than providing individual tables as separate documents. In addition, the tables should follow the most current model bioequivalence tables. **Resolved in seq0023**

APPEARS THIS WAY ON ORIGINAL

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE (API)

21 CFR 314.94(a)(9)(i) | 21 CFR 314.50(d)(1)(i)

3.2.S.1	<p>Select <u>General Information</u> (May not refer to DMF)</p> <p>3.2.S.1.1 Nomenclature</p> <p>3.2.S.1.2 Structure</p> <p>3.2.S.1.3 General properties</p> <hr style="border-top: 1px dotted black;"/> <p>Comments</p>										
3.2.S.2.1	<p>Select <u>Manufacturer</u> Drug substance (API)</p> <p>Must correlate to the establishment information submitted in annex to Form FDA 356h</p> <ol style="list-style-type: none"> 1. Name and full address(es) of the facility(ies) 2. Contact name, phone and fax numbers, email address 3. U.S. Agent's name (if applicable) 4. Specify function or responsibility 5. Type II DMF number(s) for API(s) 6. Central file number (CFN), facility establishment identifier (FEI), or data universal number system (DUNS) number (if available) 7. Additional sources of API and information (1 through 6, if applicable) <hr style="border-top: 1px dotted black;"/> <div style="background-color: #cccccc; height: 200px; width: 100%;"></div> <p style="text-align: right; font-size: small;">(b) (4)</p>										
3.2.S.3	<p>Select <u>Characterization</u></p> <p>All potential impurities should be listed in tabular format</p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th style="width: 25%;">IUPAC Chemical Name</th> <th style="width: 15%;">Code #</th> <th style="width: 20%;">Chemical Structure</th> <th style="width: 20%;">Process/ Degradation Impurity</th> <th style="width: 20%;">Source/ Mechanism</th> </tr> </thead> <tbody> <tr> <td style="height: 20px;"> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table> <p>http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalsApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf</p> <hr style="border-top: 1px dotted black;"/> <p>Comments</p>	IUPAC Chemical Name	Code #	Chemical Structure	Process/ Degradation Impurity	Source/ Mechanism					
IUPAC Chemical Name	Code #	Chemical Structure	Process/ Degradation Impurity	Source/ Mechanism							
<u>Control of Drug Substance (API)</u>											
3.2.S.4	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 10%; text-align: center; vertical-align: top;">3.2.S.4.1</td> <td style="padding: 5px;"> <p>Select <u>Specification</u></p> <p>Testing specifications and data</p> <hr style="border-top: 1px dotted black;"/> <p>Comments</p> </td> </tr> </table>	3.2.S.4.1	<p>Select <u>Specification</u></p> <p>Testing specifications and data</p> <hr style="border-top: 1px dotted black;"/> <p>Comments</p>								
3.2.S.4.1	<p>Select <u>Specification</u></p> <p>Testing specifications and data</p> <hr style="border-top: 1px dotted black;"/> <p>Comments</p>										

3.2.S.4.2

Select Analytical Procedures

Comments

Select Validation of Analytical Procedures

(API that meets United States Pharmacopeia (USP) standards or reference made to DMF, **MUST** provide verification of USP or DMF procedures)

- Select** 1. Spectra and chromatograms for reference standards and test samples (*ref. std. can be located in 3.2.S.5*)
- NO** 2. Samples-statement of Availability and Identification (21 CFR §314.50(e)(1))
- a. Name of drug substance

3.2.S.4.3

Did not provide sample statement. Resolved in seq0023

DRUG SUBSTANCE		
Name	ANI Pharmaceuticals, Inc.'s Lot No.	(b) (4)
Erythromycin Ethylsuccinate USP	18788	

Batch Analysis

- YES** 1. Certificate of analysis (COA) specifications and test results from drug substance manufacturer(s)
- YES** 2. Drug product manufacturer's certificate of analysis
API lot numbers API lot numbers

3.2.S.4.4

Acceptable

Provided one drug subst

3.2.S.4.4 Batch Analysis

(b) (4)

CONFIDENTIAL

3.2.S.4.4 BATCH ANALYSIS (ERCROS S.A., DMF NO. (b) (4))

DRUG SUBSTANCE		
Name	ANI Pharmaceuticals, Inc.'s Lot No.	(b) (4)
Erythromycin Ethylsuccinate USP	18788	

Justification of Specifications

All potential impurities should be listed in tabular format

3.2.S.4.5

Select Specified identified impurities:

Chemical Name	Code #	MDD	QT (%)	QT (TDI)	Regulatory QT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)

Select

Specified unidentified impurities:

Relative Retention Time	Code #	MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)

Select

Unspecified impurities:

MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)

		Acceptable This is a fermentation product and therefore exempt.
3.2.S.5		YES Reference standards or materials (Do NOT refer to DMF) Acceptable; provided info
3.2.S.6		Select Container closure systems Comments
3.2.S.7		Stability Select 1. Retest date or expiration date of API(s) Comments

3.2.P DRUG PRODUCT

21 CFR 314.94(a)(9)(i) | 21 CFR 314.50(d)(1)(ii)

3.2.P.1	Description and Composition of the Drug Product
	<p>YES 1. Unit composition with indication of the function of the inactive ingredient(s)</p> <p>YES 2. Inactive ingredient(s) and amount(s) are appropriate per Inactive Ingredient Database or Guide (IID or IIG) (per/dose, unit, or maximum daily dose (MDD) justification) (provide justification in a tabular format)</p> <p>3. Formulation</p> <p>N/A Oral Tablet and Oral Capsules: % to mg/dosage unit</p> <p>YES Oral suspensions and oral solutions: % to mg/dose (b) (4)</p> <p>N/A Parenterals: same unit of measure as RLD</p> <p>N/A 4. Elemental iron: provide daily elemental iron calculation pursuant to 21 CFR 73.1200 (calculation of elemental iron intake based on (MDD) of the drug product is preferred if this section is applicable)</p> <p>N/A 5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be qualitatively and quantitatively the same (Q1/Q2 same) and must be provided in the package configuration</p>
	<p>Acceptable</p> <p>We note that you provided the "Drug Product Formulation" <u>after reconstitution</u>. (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>

Formulation of Generic:

		Description of manufacturing process and process controls
	3.2.P.3.3	<p>YES 1. Description of the manufacturing process and (for aseptic fill products) facility</p> <p>YES 2. Master production batch record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified</p> <p>YES 3. Master packaging records for intended marketing container(s)</p> <p>4. If sterile product N/A</p> <p>YES 5. Reprocessing Statement (cite 21 CFR 211.115) from applicant</p> <p>Acceptable</p>
	3.2.P.3.4	<p>YES Controls of critical steps and intermediates</p> <p>Acceptable</p>
	3.2.P.3.5	<p>Process validation and/or evaluation</p> <p>1. Terminally sterilized product</p> <p>N/A <ul style="list-style-type: none"> Is this pharmacy bulk? (Go to 1.14.1.4) </p> <p>2. Aseptically filled product</p> <p>N/A <ul style="list-style-type: none"> Validation (bacterial retention studies) of sterilizing grade filter(s) </p> <p>N/A <ul style="list-style-type: none"> Is this pharmacy bulk? (Go to 1.14.1.4) </p> <p>Comments</p>

Copy and Paste Bacterial Retention Filter Validation table

Controls of excipients (inactive ingredients)		
	*	<p>Select Source of Inactive Ingredients Identified</p> <p>Comments</p>
3.2.P.4	3.2.P.4.1	<p>Specifications</p> <p>Select 1. Testing specifications (including identification and characterization)</p> <p>Select 2. Supplier's COA (specifications and test results)</p> <p>Not provided</p>
	3.2.P.4.2	<p>Select Analytical procedures</p> <p>Comments</p>

3.2.P.4.3	Select Validation of Analytical procedures Comments
3.2.P.4.4	Justification of specifications (as applicable) Select Applicant COA Not provided <u>Excipients</u> The drug product formulations for the two new strengths, 200 mg/5 mL (35 Day In-Use) and 400 mg/5 mL (35 Day In-Use), is qualitatively the same as what is currently approved in the 200 mg/5 mL (10 Day In-Use) product. There are no changes being proposed to the approved suppliers, specifications or controls for each of the inactive ingredients that are currently filed to this ANDA. Therefore, there are no respective documentation filed in Module 3.2.P.4.

Controls of drug product

3.2.P.5.1	Select Specification(s) Comments																
3.2.P.5.2	Select Analytical procedures Comments																
3.2.P.5	<p>YES Validation of analytical procedures (if using USP procedure, must provide verification of USP procedure) Samples - Statement of Availability and Identification (21 CFR §314.50(e)(1))</p> <p>YES Finished dosage form</p> <hr/> <p>Acceptable Provided sample statement.</p> <p><u>STATEMENT OF AVAILABILITY and IDENTIFICATION</u></p> <p>In accordance with 21 CFR § 314.94(a)(11), samples of the exhibit drug product, Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL (35 Day In-Use), manufactured by ANI Pharmaceuticals, Inc. at the proposed commercial manufacturing site will be made available to the FDA upon request..</p> <table border="1" data-bbox="354 1297 1490 1648"> <thead> <tr> <th colspan="4">ANI'S DRUG PRODUCT</th> </tr> <tr> <th>NDC No.</th> <th>Product</th> <th>Strength</th> <th>Lot No.</th> </tr> </thead> <tbody> <tr> <td>62559-630</td> <td>Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use)</td> <td>200 mg/5 mL</td> <td>C-1127-71</td> </tr> <tr> <td>62559-631</td> <td>Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use)</td> <td>400 mg/5 mL</td> <td>C-1127-72</td> </tr> </tbody> </table>	ANI'S DRUG PRODUCT				NDC No.	Product	Strength	Lot No.	62559-630	Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use)	200 mg/5 mL	C-1127-71	62559-631	Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use)	400 mg/5 mL	C-1127-72
ANI'S DRUG PRODUCT																	
NDC No.	Product	Strength	Lot No.														
62559-630	Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use)	200 mg/5 mL	C-1127-71														
62559-631	Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use)	400 mg/5 mL	C-1127-72														
3.2.P.5.4	<p>Batch Analysis</p> <p>YES Certificates of Analysis for finished dosage form Lot numbers and strength of drug product(s) List of lot numbers and strength of drug products</p> <hr/> <p>Acceptable</p>																
3.2.P.5.5	<p>YES Characterization of impurities</p>																

All potential degradation products should be listed in a tabular format

IUPAC Chemical Name	Code #	Chemical Structure	Degradation Product	Source/Mechanism

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovedApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf>

Comments

Justification of specifications

All potential degradation products should be listed in tabular format

YES Specified identified degradation products (shelf life):

Chemical Name	Code #	MDD	QT (%)	QT (TDI)	Regulatory QT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)

N/A Specified unidentified degradation products:

Relative Retention Time	Code #	MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)

YES Unspecified degradation products:

MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Not acceptable if proposed AC (%) > Regulatory IT Threshold (%)

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovedApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf>

Acceptable

3.2.P.5.6

(b) (4)

3.2.P.7	<p>Container closure system</p> <p>YES 1. Summary of Container/Closure System (data should be provided for each resin)</p> <p>YES 2. Components Specification and Test Data</p> <p>YES 3. Packaging Configurations and Sizes</p> <p>4. Container/Closure Testing (recommended additional testing for all plastic)</p> <p>YES a. Solid Orals: water permeation, light transmission</p> <p>N/A b. Liquids: leachables, extractables, light transmission</p> <p>N/A i. Injectables with rubber stoppers: extractables</p> <p>Select 5. Source of supply and suppliers address</p> <hr/> <p>Acceptable Same container closure system with the exception of the size of the bottle. Provided the vapor transmission tests on the HDPE bottle Did not provide light transmission tests for the HDPE bottle</p> <p>In support of the proposed container closure system, all supportive documentation for the components have been summarized and provided in this section. The DMF Letters of Authorization in Module 1.4.1 References were previously submitted in PAS S034; moreover, the containers closure system of the filed 10 Day In-Use product and the proposed 35 Day In-Use product are the same with the exception of the size of the bottle.</p>	

Copy and paste screenshot of packaging configuration and sizes

The table below summarizes the proposed container closure system for the drug product.



		Stability
3.2.P.8	3.2.P.8.1	<p>Stability summary and conclusion (finished dosage form)</p> <p>YES 1. Stability protocol submitted</p> <p>2. Expiration dating period for marketed packaging 24 m</p> <p>3. Expiration dating period for bulk packaging (if applicable) Expiration date</p>

	Acceptable
3.2.P.8.2	<p>Post-Approval Stability Protocol and Stability Commitment</p> <p>YES 1. Post-Approval Protocol and Commitment from applicant http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120979.pdf</p>
	Acceptable
3.2.P.8.3	<p>Stability Data (Refer to the Final Guidance for Industry ANDAs: <i>Stability Testing Drug Substances and Products</i>, dated June 2013)</p> <p>YES 1. 1 batches?</p> <p>YES a. One API lots used per strength?</p> <p>YES b. All presentations of container closure systems amongst the 3 batches?</p> <p>N/A 2. Additional stability data to support additional API sources (if applicable)</p> <p>3. Data- At minimum, 3 months and 4 time points</p> <p>YES a. Accelerated</p> <p>NO 1. Significant change occurred</p> <p>N/A 2. If yes, 6 months intermediate stability data</p> <p>YES b. Long term storage (Room Temperature)</p> <p>YES 4. Batch numbers on stability records the same as the test batch</p> <p>5. Stability study initiated</p> <p>YES a. Accelerated</p> <p>N/A b. Intermediate (if applicable)</p> <p>YES c. Long Term</p> <p>6. Date stability sample removed from stability chamber for each testing time point</p> <p>YES a. Accelerated</p> <p>N/A b. Intermediate (if applicable)</p> <p>YES c. Long Term</p> <p>N/A 7. For liquid and semi-solid products, upright and inverted/horizontal storage orientation</p> <p>Acceptable</p> <p>Minimum 1 batch, 3 months' worth of acc(4 time points) and LT (2 time points) data. Using only 1 api lot: acceptable</p> <p>In module 3.2.P.8.3, provide the withdrawal (pull) dates for each time point for your long-term stability studies (including all batches, conditions, and packaging configurations) in both the "Stability Data" file and the individual data tables. Resolved in seqq0023</p>

3.2.S.4.4 Batch Analysis (b) (4)

CONFIDENTIAL

3.2.S.4.4 BATCH ANALYSIS (ERCROS S.A., DMF NO. (b) (4))

DRUG SUBSTANCE		
Name	ANI Pharmaceuticals, Inc.'s Lot No.	(b) (4)
Erythromycin Ethylsuccinate USP	18788	(b) (4)

STATEMENT OF AVAILABILITY and IDENTIFICATION

In accordance with 21 CFR § 314.94(a)(11), samples of the exhibit drug product, Erythromycin Ethylsuccinate for Oral Suspension USP, 200 mg/5 mL and 400 mg/5 mL (35 Day In-Use), manufactured by ANI Pharmaceuticals, Inc. at the proposed commercial manufacturing site will be made available to the FDA upon request..

ANI'S DRUG PRODUCT			
NDC No.	Product	Strength	Lot No.
62559-630	Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use)	200 mg/5 mL	C-1127-71
62559-631	Erythromycin Ethylsuccinate for Oral Suspension USP (35 Day In-Use)	400 mg/5 mL	C-1127-72

3.2.R REGIONAL INFORMATION

21 CFR §314.50(d)(1)(ii)(b)

REGIONAL INFORMATION (DRUG PRODUCT)	
3.2.R.P Drug Product	<p>1. Executed batch records</p> <p>YES Copies of executed batch records with equipment specified, including packaging records (packaging and labeling procedures) (Refer to batch size and packaging information that meet the minimum threshold amount for specified dosage forms, i.e., solid oral dosage forms, oral powders/solutions/suspensions, parenteral drug products, ophthalmic/otic drug products, transdermal patches, topicals (i.e., creams, lotions, gels, inhalation solutions, nasal sprays, etc.). Refer to the guidance for industry, <i>ANDAs: Stability Testing Drug Substances and Products, Questions and Answers</i> (May 2014)</p> <p style="margin-left: 20px;">a. Two (2) pilot scale and one (1) small scale OR</p> <p style="margin-left: 20px;">b. Three (3) pilot scale</p> <hr style="border-top: 1px dotted black;"/> <p>Acceptable</p> <p>YES Batch reconciliation and label reconciliation</p> <p style="margin-left: 20px;">a. Theoretical yield Theoretical yield</p> <p style="margin-left: 20px;">b. Actual yield Actual yield</p> <p style="margin-left: 20px;">c. Packaged yield Packaged yield</p> <hr style="border-top: 1px dotted black;"/> <p>Acceptable Actual yields were provided within the batch records.</p> <p style="color: red; margin-left: 20px;">Provide the Executed Batch Reconciliation tables to include theoretical, actual, and packaged yield. Theoretical, actual, and packaged yield should also be expressed in units of measure. Resolved in seq0023</p> <hr style="border-top: 1px dotted black;"/> <p>Bulk package reconciliation for all bulk packaging considered a commercial container is recommended if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections:</p> <p>Select a. Bulk package label (1.14.1)</p> <p>Select b. Bulk package stability (3.2.P.8)</p> <p style="margin-left: 20px;">Select 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months</p> <p style="margin-left: 20px;">Select 2. If bulk is only warehoused for repackaging, provide room temperature stability data at 0,3,6 months</p> <p style="margin-left: 20px;">Select c. Bulk package container closure information (3.2.P.7)</p> <hr style="border-top: 1px dotted black;"/> <p>Comments</p> <hr style="border-top: 1px dotted black;"/> <p>Select Information on components <i>Name(s) and address(es) of the API, inactive ingredient(s), and containers and closures in tabular format. Hyperlinks are sufficient.</i></p> <hr style="border-top: 1px dotted black;"/> <p>Comments</p> <hr style="border-top: 1px dotted black;"/> <p>3.2.R.3.P Select Methods validation package Methods validation package (Required for Non-USP drugs)</p> <hr style="border-top: 1px dotted black;"/> <p>Comments</p>

MODULE 5: CLINICAL STUDY REPORTS

21 CFR 314.94(a)(7)

5.2	<p>YES <u>Tabular listing of clinical studies</u> http://www.fda.gov/ucm/groups/fdagov-public/%40fdagov-drugs-gen/documents/document/ucm073290.pdf</p> <p>Acceptable In module 5.2 , file “ Erythromycin Ethylsuccinate for Oral Suspension BE Companion Document”, the applicant provides justification on why analytical studies and data was not provided on both analytes per the PSG and that this is considered a technical review based on the applicant’s statement.</p>
5.3	<p>BA/BE</p> <p>YES N/A</p> <ol style="list-style-type: none"> 1. Formulation data same? <ol style="list-style-type: none"> a. Comparison of all strengths (proportionality of multiple strengths) b. Parenterals, ophthalmics, otics and topicals (21 CFR 314.94 (a)(9)(iii)-(v)) 2. Lot numbers and strength of products used in BE study(ies) 3. In vivo pharmacokinetic (PK) study(ies) 4. In vivo BE study(ies) with clinical endpoint(s) 5. In vivo BE study(ies) with pharmacodynamics (PD) endpoints (pilot and pivotal vasoconstrictor) 6. In vitro binding study(ies) 7. Nasal products (May contain a clinical endpoint or PK study) 8. Biopharmaceutics Classification System (BCS) 9. In-Vitro Feeding Tube Testing 10. Pressurized Metered Dose Inhalation Products <p>(Continue with the appropriate study type box below)</p> <p>Acceptable</p>
Study Type	<p>Miscellaneous</p> <p>Select 1. Drug Efficacy Study Implementation (DESI) Drug Product (in Module 2.7)</p> <p>Select a. Table 5 Dissolution</p> <p>Select b. Table 6 Formulation data</p> <p>Select 2. Quantitative capsule rupture testing (liquid-filled capsule products)</p> <p>Select a. Study report</p> <p>Select b. Release profile per the drug product specific guidance (demonstrates the time points at which 80% of the drug is released from the capsule)</p> <p>Select c. Apparatuses and the respective parameters as recommended per the drug product specific guidance</p> <p>Select 3. In vitro release tests (specifically for acyclovir ointment and some ophthalmic suspensions)</p> <p>Select a. 90% confidence interval (CI) within 75-133% for 8th and 29th (first stage)</p> <p>Select b. 90% CI within 75-133% for 100th and 215th (second stage, if first stage failed)</p> <p>Select c. Study report</p> <p>Select d. Chromatograms/histograms</p> <p>Select e. Raw data</p> <p>Select 4. In vitro comparative physicochemical data</p> <p>Select 5. In vitro microbial kill test</p>

Effective as of December 11, 2017

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>
 For a Comprehensive Table of Contents Headings and Hierarchy please go to: <http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>
 Draft Guidance for Industry ANDA Submissions – Content and Format of Abbreviated New Drug Applications:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf>

2.7 Clinical Summary

2.7	<p>Clinical Summary (Bioequivalence) Model BE Data Summary Tables http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf</p> <p>YES E-Submission: PDF YES MS Word</p> <p>2.7.1 Summary of biopharmaceutic studies and associated analytical methods</p> <p>2.7.1.1 Background and overview</p> <p>YES Table 1. Submission summary YES Table 4. Bioanalytical method validation YES Table 6. Formulation data YES Table 10. Study information NO ■ Long-term stability studies (LTSS) data location and hyperlink YES Table 11. Product information N/A Table 17. Comparative physicochemical data of ophthalmic solution products</p>
	<p>Acceptable</p> <p>Missing hyperlink to long-term stability studies data location .</p> <p>Address the following in module 2.7:</p> <ol style="list-style-type: none"> a. Per the Model Bioequivalence Data Summary Tables located at, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf <ol style="list-style-type: none"> i. Table 10 (Study Information) should identify all analytes along with the long-term storage stability information and include the exact location of the LTSS study reports and data, including module, section, subsection and page(s). Provide (a) working hyperlink(s) to the locations as appropriate. Resolved in seq0023 ii. Table 4 (Bioanalytical Method Validation) should be provided for each analyte (free base and total erythromycin) Resolved in seq0023

ii. Table 4 (Bioanalytical Method Validation analyte (free base and total erythromycin

Provided in the original PAS was ANI's justification for the analytes measured in the submitted bioequivalence studies in addition of these new strengths. The *Companion Bioequivalence for Erythromycin Ethylsuccinate* (June 2018) review aid to assist in explaining ANI's position on the published BE Guidance on the Erythromycin Ethylsuccinate

The document concludes that the wording of the ethylsuccinate granules for oral suspension (June 2018) clearly describe the Agency's true thinking and recommendations for guidance and an accurate measurement of bioequivalence only total erythromycin in bioequivalence studies for the bioequivalence studies included in this submission located in **Module 2.7** and **Module 5.2**. **Therefore**, and is provided in the summary tables, such as Table 5.

It is also important to note, that this justification and knowledge, has been accepted by the FDA in our feedback (number 606-17) submitted for this same product line (Feb. 14, 2018).

2.7.1.2 Summary of results of individual studies

- YES Table 5. Summary of in vitro dissolution
 - YES
 - Comparative in vitro dissolution data (individual)
 - N/A
 - Alcohol dose dumping dissolution (if applicable)
 - N/A
 - ½ tablet dissolution (if applicable)
 - YES
 - COA for test and reference products of the bioequivalence (BE) strength (should include potency, assay, content uniformity, date of manufacture and lot number)
- YES Table 9. Reanalysis of study samples
- YES Table 12. Dropout information
- YES Table 13. Protocol deviation
- YES Table 14. Summary of standard curve and quality control (QC) data for BE sample analysis

Acceptable

No summary dissolution study table for 200mg/5 ml vs 400mg/5ml (test vs test), but provided the individual dissolution data.

2.7.1.3 Comparison and analyses of results across studies

- YES Table 2. Summary of bioavailability (BA) studies
- Table 3. Statistical summary of the comparative BA data:
 - YES 1. Unscaled average – Table A
 - YES 2. Reference-scaled average BE studies – Tables A and B BE Studies
- YES Table 16. Composition of meal used in fed bioequivalence study

Acceptable

The study title listed in Table 3 (Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE Studies) does not match its respective study number. Please revise

accordingly. Resolved in seq0023

2.7.1.4 Appendix

YES Table 15. Standard operating procedures (SOPs) regarding bioanalytical repeats of study samples

Acceptable

2.7.4 Summary of clinical safety

2.7.4.1.3 Demographic and Other Characteristics of Study Population

YES Table 7. Demographic profile of subjects completing the bioequivalence study

Acceptable

2.7.4.2.1.1 Common Adverse Events

YES Table 8. Incidence of adverse events in individual studies

Acceptable

Dissolution Guidance from USP or FDA webpage

Search Results for: "erythromycin"

CSV Excel Filter:

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Erythromycin	Tablet			Refer to USP			12/24/2015
Erythromycin	Tablet (Delayed Release)			Refer to USP			10/31/2013
Erythromycin Ethylsuccinate	Oral granule			Develop a dissolution method			06/30/2016
Erythromycin Ethylsuccinate	Suspension	II (Paddle)	75	Monobasic Sodium Phosphate, pH 6.8 Buffer with 1% SLS Buffer w/ 1% SLS	900	10, 20, 30, 45 and 60	01/27/2004

Copy and Paste Table 17, if applicable

5.3.1.2 and 5.3.1.4

YES	BE Study(ies) per the Recommendations in the Individual Product BE Guidance
Acceptable	
	Clinical Report
YES	Fasting
YES	Fed
Select	Other
Acceptable	
	Individual and Mean Data
YES	Fasting
YES	Fed
Select	Other
Acceptable	
	Graphs, Linear, & Ln
YES	Fasting
YES	Fed
Select	Other
Acceptable	
	SAS Datasets
YES	Fasting
YES	Fed
Select	Other
Acceptable	
	Statistical Report (including SAS Output)
YES	Fasting
YES	Fed
Select	Other
Acceptable	
	Method Validation Report

YES	Fasting
YES	Fed
Select	Other
Acceptable	
LTSS Data	
YES	Fasting
YES	Fed
Select	Other
Acceptable	
Study Bioanalytical or Analytical Report	
YES	Fasting
YES	Fed
Select	Other
Acceptable	
Chromatograms, 20%	
YES	Fasting
YES	Fed
Select	Other
Acceptable	
Raw Numerical Data	
YES	Fasting
YES	Fed
Select	Other
Acceptable	

N/A Clinical Endpoint(s)

2.7 Clinical Summary

2.7	Clinical Endpoint Summary Tables	
	http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM400548.pdf	
	Select	E-Submission: PDF
	Select	MS Word
	Select	Table 1. Submission summary
	Select	Table 2. Summary of clinical endpoint bioequivalence (BE) studies
	Select	Table 3. Summary of skin irritation/sensitization/adhesion study(ies)
	Select	#1 Skin irritation/sensitization/adhesion study(ies)
	Select	#2 Adhesion data from PK study
	Select	#3 Adhesion study
	Select	Table 4. Study center information
	Select	Table 5. Study inclusion/exclusion criteria
	Select	Table 6. Prohibited concomitant medication list
	Select	Table 7. Product information
	Select	Table 8. Study schedule (for example)
Select	Table 9. Study populations (general)	
Select	Table 10. Subject populations (specific for Nasal Spray Products)	
Select	Table 11. Subject populations (specific for skin irritation/sensitization/adhesion studies)	
Select	Table 12. Summary of protocol deviations	
Select	Table 13. Summary of patient discontinuation/early termination from the study	
Select	Table 14. Demographic characteristics at baseline for the safety population, modified	

		intention to treat (M)ITT population, and per protocol population
Select	Table 15.	Primary endpoint analysis result for a clinical endpoint BE study
	Table 16.	Non-inferiority analysis result for a skin irritation/sensitization/adhesion study
Select		A. Irritation and adhesion scores
Select		B. Sensitization analysis
	Table 17.	Frequency tables (specific for skin irritation/sensitization/adhesion studies)
Select		A. Irritation scores(combined irritation and other effect scores) for per protocol population
Select		B. Adhesion scores for per protocol population
Select		C. Irritation scores (combined irritation and other effect scores) for per protocol population during challenge period/re-challenge period
Select	Table 18.	Patch removal or move date due to significant skin irritation (specific for skin irritation/sensitization/adhesion studies)
Select	Table 19.	Proportion of subjects with adhesion score of 2 or more and 3 or more per treatment (specific for skin irritation/sensitization/adhesion studies)
Select	Table 20.	Summary of adverse events
Select	Table 21.	Formulation
Select		a. For a waiver of BE study requirements or for a test product that requires qualitative and quantitative sameness to the reference listed drug (RLD)
Select	Table 22	OGD excipient/impurity toxicology data table
	Comments	

Gaines, Tangela

From: Gaines, Tangela
Sent: Monday, June 18, 2018 12:03 PM
To: 'ellen.camos@anipharmaceuticals.com'
Cc: ANDAFiling
Subject: ANDA 062055/S-35 Filing Review Comments

Dear Ellen Camos:

This electronic mail is in reference to ANDA 062055-Supplement-35 submitted on May 25, 2018 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

SPECIAL INSTRUCTIONS:

- We request that you acknowledge the receipt of this email correspondence.
 - Provide a complete response to all of the items identified below **within 7 calendar days** from the date of this communication.
 - If a complete response is not submitted to the ANDA and received within 7 calendar days, the application will be deemed incomplete and will be refused for receipt.
 - Your response should contain a point-by-point reply to each of the identified comment(s) with corresponding hyperlink(s), where applicable, to the body of data within the ANDA.
 - You should notify me via email or telephone when you have submitted your response.
 - Your cover letter should clearly indicate **Filing – Response to Information Request**.
 - Any questions or need for clarification with respect to any of the following deficiencies can be sent to me, the project manager assigned to this ANDA during filing review. A teleconference may be requested within 1 business day of this email. With your request, you must clearly identify your question(s). **(Note: The teleconference will be limited to a discussion of only the questions provided in your teleconference request. Also, your query does not place a hold on the timeframe in which the response must be submitted, as per bullet 2.)**
1. Correct the following on Form FDA 356h:
 - a. Revise Field 13 to include all proposed strengths.

Note: Provide a fillable PDF copy of the 356h in all your submissions if you are submitting a scanned signed copy of the 356h, otherwise the omission of the fillable PDF copy of the 356h will be counted as a deficiency.

Best Regards,

LT Tangela Gaines, PA-C
Unites States Public Health Service
Project Manager-Division of Filing Review
FDA/CDER/OGD/ORO/DFR
10903 New Hampshire Avenue, Bldg. 75
Silver Spring, MD 20993
Tangela.Gaines@fda.hhs.gov



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APPEARS THIS WAY ON
ORIGINAL

Gaines, Tangela

From: Gaines, Tangela
Sent: Friday, June 08, 2018 2:02 PM
To: 'ellen.camos@anipharmaceuticals.com'
Cc: ANDAFiling
Subject: ANDA 062055/S-35 Filing Review Comments

Dear Ellen Camos:

This electronic mail is in reference to ANDA 062055/S-35 submitted on May 25, 2018 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

SPECIAL INSTRUCTIONS:

- We request that you acknowledge the receipt of this email correspondence.
 - Provide a complete response to all of the items identified below **within 7 calendar days** from the date of this communication.
 - If a complete response is not submitted to the ANDA and received within 7 calendar days, the application will be deemed incomplete and will be refused for receipt.
 - Your response should contain a point-by-point reply to each of the identified comment(s) with corresponding hyperlink(s), where applicable, to the body of data within the ANDA.
 - You should notify me via email or telephone when you have submitted your response.
 - Your cover letter should clearly indicate **Filing – Response to Information Request**.
 - Any questions or need for clarification with respect to any of the following deficiencies can be sent to me, the project manager assigned to this ANDA during filing review. A teleconference may be requested within 1 business day of this email. With your request, you must clearly identify your question(s). **(Note: The teleconference will be limited to a discussion of only the questions provided in your teleconference request. Also, your query does not place a hold on the timeframe in which the response must be submitted, as per bullet 2.)**
1. In module 2.3, provide a Quality Overall Summary (in both MS Word and PDF format) for the drug product, that adheres to the Question-Based Review format.
 2. Address the following in module 2.7:
 - a. Per the Model Bioequivalence Data Summary Tables located at, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf>
 - i. Table 10 (Study Information) should identify all analytes along with the long-term storage stability information and include the exact location of the LTSS study reports and data, including module, section, subsection and page(s). Provide working (a) working hyperlink(s) to the locations as appropriate.
 - ii. Table 4 (Bioanalytical Method Validation) should be provided for each analyte (free base and total erythromycin)
 - b. Per the guidance for industry entitled, *M2 eCTD: Electronic Common Technical Document Specification* located on the internet, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073240.pdf>, module 2.7.1 and 2.7.4 “should consist of a single file” (MS Word and PDF format) rather than providing individual tables as separate documents. In addition, the tables should follow the most current model bioequivalence tables.

3. Provide a samples-statement of availability and identification in module 3.2.S.4.3.
4. We note that you provided the “Drug Product Formulation” after reconstitution. (b) (4)
(b) (4)
(b) (4)
5. In module 3.2.R, provide the Executed Batch Reconciliation tables to include theoretical, actual, and packaged yield. Theoretical, actual, and packaged yield should also be expressed in units of measure (i.e. number of bottles).
6. In module 3.2.P.8.3, provide the withdrawal (pull) dates for each time point for your long-term stability studies (including all batches, conditions, and packaging configurations) in both the “Stability Data” file and the individual data tables.

Additional Comment:

The study title listed in Table 3 (Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE Studies) does not match its respective study number. Please revise accordingly.

Note: Provide a fillable PDF copy of the 356h in all your submissions if you are submitting a scanned signed copy of the 356h, otherwise the omission of the fillable PDF copy of the 356h will be counted as a deficiency.

Best Regards,

LT Tangela Gaines, PA-C
Unites States Public Health Service
Project Manager-Division of Filing Review
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